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From Methodologic Guidelines for Reports of Clinical Trials (Cancer Treat Rep 69:1-3, 1985).

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EDITORIAL

Paying for Patient Care in Treatment Research—Who Is Responsible?[1]

Robert E. Wittes[2,3,*]

The worth of biomedical research is an axiom of modern life. In addition to the intellectual gratification that accompanies any type of research, the practical benefits of effective prevention or treatment of disease have obvious appeal both to the research community itself and to society generally. Although medical research is certainly not without its ethical and philosophical dilemmas, these have never seriously jeopardized public support for the whole enterprise. Most seem to feel that the lessening of suffering through the conquest of disease does not require elaborate justification. In addition, the economic motives for developing effective therapies have been an ample incentive for industry. The result has been a rather large-scale investment in biomedical research that has paid off handsomely in such areas as the development of effective prophylaxis against polio and measles, the conquest of many formerly fatal infectious diseases, the development of organ transplantation, and a substantial reduction in mortality from many kinds of cancers.

We find ourselves now at a most exciting juncture in clinical cancer research. The pace of progress in basic biology has increased dramatically, to an extent that could not have been foreseen even as recently as a decade ago. Fundamental advances have resulted in much more compelling therapeutic hypotheses. The enhanced possibilities for the development of rational therapeutic strategies, coupled with the demonstrated profit potential of systemic cancer treatment, have impelled the pharmaceutical industry to devote increasing resources to this area.

On the other hand, some powerful countervailing forces threaten the pace of progress. Over the past few years, the nation has become appropriately concerned with the spiraling cost of medical care. The federal government, the insurance industry, and many elements of the health care delivery system itself are exploring various approaches to cost containment. To the extent that research treatments are more costly than conventional care, therefore, research priorities will face mounting pressures from the general effort to control medical costs. If prospective payment systems lead to an increasing emphasis on ambulatory care, it may be more difficult to study intensive treatment approaches that require inpatient support. The full investigation of innovative treatment strategies may thus be compromised.

Second, most insurance contracts explicitly exclude investigational treatment from reimbursement. Most policies require that reimbursable treatment have established value as therapy by the standards of the community in which it is applied. This stance obviously serves to decrease the outlays of the insurance company and thus enables it to optimize its competitive position by offering subscribers reasonable coverage at the lowest possible cost. In addition, this position makes it possible for third-party carriers to avoid paying for every sort of shady new ministration conveniently labeled "research" by its advocates.

We are all aware that the exclusion of investigative therapy from reimbursement has not been rigorously enforced, probably because of the difficulty in ascertaining whether a treatment is investigational or not from the information on claims forms. The result has been that the insurance industry has been a most important, if at times unwitting, partner in a substantial volume of clinical research.

Unhappily, anecdotes suggest that things may be changing. Ambulatory patients treated on investigational phase II protocols have on occasion been denied coverage for hospitalizations necessitated by neutropenia and fever from the drug; the justification for such denials is apparently that if the agent itself is not of "proved value," then the possible medical consequences of using it are not reimbursable. The practice of preadmission approval for certain kinds of hospitalizations, particularly those involving costly therapeutic maneuvers such as high-dose chemotherapy with bone marrow transplantation, often results in denial. As the pressure to control escalating health care costs increases, insurance companies can be expected to increase their level of scrutiny of claims.

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[2] Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

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* *Reprint requests to:* Robert E. Wittes, MD, Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Landow Bldg, Rm 4A22, National Institutes of Health, Bethesda, MD 20892.

Third, at a time when the federal government seems committed to reducing its massive budget deficits, all areas of federal spending will come under intensive examination. Current indications are that the government will continue to see biomedical research as a major national priority, but at present it is simply not clear what the net impact of deficit reduction measures will be upon the National Institutes of Health (NIH) and by implication on the whole biomedical research effort.

Improved therapy may result from insight into mechanism or from serendipitous discovery; in either case, the final common pathway for testing new treatments is a clinical experiment with patients as the subjects. Whether the experiment is the administration of a new drug to a few patients in a single center or a large multicenter randomized trial involving thousands of subjects, our ability to administer experimental therapy is fundamental to medical progress. If we cannot test new treatments, the state of the art will freeze at its present level. To the extent that a constraining of resources forces us to pursue promising scientific areas at a less than maximal rate, progress will also be submaximal.

While clinical trials are obviously necessary, they are also expensive. Currently the National Cancer Institute (NCI) spends about $60 million annually in support of a large clinical trials network capable of studying a wide variety of unresolved questions in therapy. At a time when therapeutic possibilities hold greater promise than ever before, a vigorous clinical trials capability has never been more important. The fostering of clinical trials research is a shared endeavor for which all interested parties must take explicit and purposeful responsibility.

WHAT TREATMENT CAN BE CLASSIFIED AS RESEARCH?

By treatment we mean any procedure performed on patients with therapeutic intent; excluded, therefore, are a variety of metabolic, pharmacologic, or epidemiologic studies that may be of scientific value but will have no direct impact on the health of the individual participant. How to define research treatment for financial and reimbursement purposes, however, particularly for a specialty like oncology, where current therapy is often unsatisfactory, is much less clear. Let us consider a few possibilities.

(*a*) Research treatment is any therapy given in the context of a prospective clinical trial for the purpose of answering an unresolved question.

(*b*) In studies involving a comparison of a new treatment with a control, research treatment is the new treatment; the control arm may be considered conventional care.

(*c*) Research treatment is any regimen involving an agent not licensed by the Food and Drug Administration (FDA) for the particular indication in question.

(*d*) Research treatment is any treatment involving an agent not yet licensed by the FDA for any indication at all.

(*e*) Research treatment is any regimen not considered to be part of the standard pattern of medical practice in the community of interest.

The very broad formulation expressed in (*a*) above is an adequate general definition of clinical treatment research. For our present purposes, however, it is not very useful. If, for example, one is comparing two very well-characterized treatments in a formal clinical trial, it makes no sense to consider these treatments research (and deny insurance coverage) if they are given in a trial, but conventional (and therefore reimbursable) if they are given outside a study setting according to the conviction, whim, or bias of an individual physician.

Definition (*b*) is somewhat more meaningful, in that it acknowledges the difference between a standard of treatment (the control arm) and an innovation (the test treatment), which is generally less well characterized than the control. Usually, however, there is a substantial body of information indicating that the test treatment may have significant advantages compared to the control. These putative advantages may be in greater efficacy, reduced toxicity, decreased cost, or some other parameter, but whatever they are, they have been persuasive enough to motivate a prospective controlled trial. Treatments that are not thought to have at least some advantages over standard treatment are not usually subjected to study.

In cancer this usually means that the test therapy has very significant credibility among substantial segments of the oncology community. If we lived in a world without clinical trials, the natural course of events would be that this credibility would translate into more widespread use of the new therapy in routine practice. At some point, on the basis of personal experience, discussion with colleagues, and retrospective analyses in the literature, individual physicians would develop their own conclusions about its place in the armamentarium. Insurance companies would still have to come to some determination about reimbursement policies for the new treatment. It seems obvious that, without rigorous standards of evidence, far more claims would be paid than is the case today.

Definition (*c*) has at least the virtue of being unambiguous; a new agent either has FDA approval for a specific indication or it does not. Probably for this reason, some individuals in the insurance industry have voiced an alarming degree of interest in this definition, which is really most unsuitable for reimbursement decision-making. Its most serious deficiency is that the absence of a labeling indication of a marketed drug for a specific disease does not imply lack of effectiveness. The filing of a supplemental New Drug Application by a pharmaceutical company to extend the indications of an already marketed agent is a complex business decision that depends on many factors other than the scientific evidence supporting the claim.

Other problems exist as well. If the patient is receiving a treatment that includes standard therapy plus a promising new investigational agent, the physician's expectation is that the addition will result in improved therapy. Preliminary data have no doubt provided some basis for this belief. There is usually little reason to think that new treatments of this type will actually be inferior to established ones, although admittedly this possibility cannot be formally ruled out a priori. If X is an experimental agent and ABC is standard treatment, therefore, it is not intuitively sensible to deny coverage for ABCX, even if the clinical data for the four-drug combination are not yet available.

In addition, use of FDA patterns of approval to establish guidelines for standard care is frustrated by the varying criteria for approval that have been employed by FDA over the years. In the area of cancer drugs specifically, some agents were approved for specific tumor types in the past on the basis of data that would not be regarded today as providing substantive support for a claim of efficacy. Use of FDA approval as a criterion would lead to the irrational situation of granting reimbursement for administration of mechlorethamine for non-small cell lung cancer, while denying it for the various cisplatin-containing combinations that have been the focus of so many recent clinical trials.

Definition (*d*) probably corresponds most closely to the modus operandi of insurance companies today. If a new agent has not yet been approved by FDA for any indication at all, then it is considered experimental for all indications. This formulation, however, leads to a rational contradiction if it just so happens that the investigational treatment is the most effective therapy available. In the past this has been the case with the therapies of a number of cancers, including the leukemias, lymphomas, testicular cancer, and small cell lung cancer. It is simply not sensible to deny an insurance claim for such treatment, while paying for one covering less effective treatment.

Definition (*e*) has, in principle at least, the virtue of depending on expert medical judgment on a case-by-case basis. For this reason alone, however, it is likely to be completely impracticable for actual implementation.

It would seem, then, that the use of the concept "investigational" as a criterion for making decisions on reimbursement is not reasonable. Far more meaningful would be a system in which medical care was reimbursed according to other criteria. We shall return to this point in more detail later.

DEFINING COSTS

The cost of a clinical trial may be divided into two general categories: the costs of caring for patients on study and the costs of doing the research itself. As we have noted, in past years most of the costs of patient care have been borne by the insurance industry.

It is obvious, however, that not all the patient care costs of research subjects are due to participation in research; a variable proportion of them would exist even if the patient were treated conventionally. This distinction between patient care costs attributable to research and those due to conventional care is clear enough in principle, and there are many situations in which it may be operationally useful as well. A patient with progressive cancer who is feeling rather well and is hospitalized solely for participation in a phase I clinical trial, instead of receiving alternative noninvestigational therapy on an ambulatory basis, clearly incurs the costs of inpatient care as a result of participating in a medical experiment.

When applied to sick patients, however, these distinctions become very blurred. Consider the following scenario. A patient with metastatic breast cancer, previously treated with standard combination chemotherapy and appropriate hormonal maneuvers, is hospitalized for progressive cancer and hypercalcemia. Institution of a saline diuresis and glucocorticoids fails to control the serum calcium adequately, so on Day 10 her physicians begin cytotoxic therapy with an investigational agent that has shown promising initial evidence of activity in breast cancer during the early phase II trials. This agent must be given by continuous infusion over 5 days. The serum calcium normalizes, and the patient is discharged 8 days after start of therapy.

How are the patient care costs to be allocated here? The first 9 days of therapy can clearly be attributed to conventional care, but what of the remaining 8? Which costs can be allocated in a rational, nonarbitrary fashion to research and which to the exigencies of standard care? This dilemma occurs every time a sick patient receives investigational therapy. To even attempt a rational allocation, an insurance carrier would have to audit all such hospital records. Since this is clearly an impossibility, the carrier's alternative, in view of the research exclusion, is simply to deny coverage for the whole hospitalization, or for the portion of it that was somehow related to (not necessarily even due to) the investigational treatment. This latter decision has no medical justification at all if in fact the investigational treatment happens to be the most promising treatment available for the particular patient. Even if the effectiveness of the treatment is unproved, the decision not to cover the costs is a very poor one if there is no good alternative conventional therapy and best medical judgment is that the experimental maneuver is the most reasonable step under the circumstances. Nevertheless, most insurance contracts actually *require* the carrier to deny such claims because of the clause excluding experimental treatment.

For its part the insurance industry will claim that the responsibility for covering patient care costs in a research setting belongs to the sponsor of the research. In fact, of course, the sponsor, whether an agency of the federal government or a pharmaceutical company, carries an enormous load in research and development costs already. In clinical trials the vast majority of these expenditures are not related to patient care but rather to the actual research costs of the project: data management, personnel, special tests, and so on. Moreover, in the case of grants from the Public Health Service (PHS), the cost-sharing arrangements specified by PHS policy have also mandated that significant research costs be shouldered by the institutions themselves. Without a vast infusion of new monies, a wholesale shift of the responsibility for patient care costs onto sponsors at this point would badly cripple the entire clinical trials effort. Possibilities for an appropriations increase of this magnitude in the present climate are, to say the least, uncertain.

WHAT SHOULD BE DONE?

No area of medicine is immune to the pernicious effects of the research exclusion. Concern with this issue is not new (1-3), and the question of whether it is appropriate for patients or their insurance companies to pay for medical care in research settings has been discussed before (4-6). In 1983 a workshop at Airlie House, sponsored by the Arthritis Foundation and the National Multiple Sclerosis Society, explored the role of third-party carriers in clinical trials of new agents (2). The recommendations from this meeting rested upon the premise that clinical trials are important in defining effectiveness, which then may help rationalize reimbursement decisions and thus may lead to reduction in the cost of care. The participants urged a stronger role for the Health Care Financing Administration (HCFA) in the funding of clinical trials and advocated the designation by the insurance industry of certain treatments as "under evaluation"; these would specifically include very expensive treatments or those regarded by knowledgeable physicians as of doubtful value or as posing serious risks. These treatments would then be suitable for third-party reimbursement when delivered in the context of a clinical trial, but not otherwise. Implementation of these and other suggestions from the Airlie House meeting might be helpful in ensuring the survival of those clinical trials that focus on major problems in cost containment, but they do not go nearly far enough in recognizing the peril to clinical research generally.

A satisfactory solution is easy to outline. A reasonable insurance system ought to reimburse all medical care that is effective, whether investigational or not. In addition, if there is only partially effective treatment or no effective treatment for a particular condition, insurance ought to pay for the patient care costs of investigational treatment that has adequate scientific justification. Conversely, insurance should not pay for treatment known to be ineffective or less than optimally effective, whether "standard" or not, nor should it reimburse for fraudulent care masquerading as medical research.

Now why should insurance cover the patient care costs of developmental therapy? Arguments that appeal to right, justice, and societal obligation are by themselves most unlikely to cut any ice in corporate boardrooms, where business decisions are generally made on somewhat more hard-nosed grounds. Nevertheless, in our eagerness to bolster the purely economic arguments for paying the costs of medical care in research settings, we should not lose sight of the nature of the health insurance industry. These companies are, after all, selling health insurance, not wrenches or furniture or petroleum. They are part of the health care delivery system. We should not assume that they are susceptible only to economic arguments. We would probably do better to assume that, like physicians and nurses, they may also make professional decisions based in part on what is in the real interests of their constituency. This is not to say that the financial bottom line is not important, or even most important, but only that it is perhaps not all-important.

Can we show skeptical insurance executives and their subscribers that support of clinical research is a good long-term investment for the industry? For example, perhaps clinical research eventually leads to treatments that are not only more effective but also cheaper.

Certainly there are striking examples of this. The prevention of poliomyelitis is vastly cheaper than the chronic care of a paralyzed victim. The availability of effective outpatient chemotherapy has made the treatment of tuberculosis much less costly than in the days of long confinement to sanitoria and frequent surgical intervention. Currently available therapy for advanced Hodgkin's disease is undoubtedly cheaper in real dollars than the markedly less effective therapy of 20 years ago, when most patients received palliative care through long and complicated downhill courses. Completely effective adjuvant chemotherapy would probably be much cheaper than the care of relapsed patients with metastatic disease.

On the other hand, one cannot argue this point uncritically. If one must treat all high-risk patients with adjuvant chemotherapy to prevent only a percentage of them from relapsing, it takes a rigorous and quantitative analysis to determine the relative *total* costs of the two treatment policies for the relevant patient population. The answer would depend not only on the relative costs of care for adjuvant versus metastatic disease patients but also on the level of effectiveness of the adjuvant treatment in preventing relapse (since this would determine the number of patients destined to develop metastatic disease). There are also admittedly many circumstances in which much more effective treatment is also much more expensive; today's state of the art for childhood acute lymphoblastic leukemia must cost much more per case than the largely palliative approaches of the past.

Throughout this discussion the costs that we have been referring to have been the costs of patient care, as borne by insurance companies. In considering the comprehensive economic benefits of better treatment to society, of course, one must include the many years of economic productivity of a cured cancer patient who is returned to the work force. This issue seems of borderline relevance to the present discussion, since it is hard to see how the policies set by an individual insurance company (or even the entire industry) would be affected by such considerations. This issue might, however, have a significant impact on the deliberations of the federal government, which should care very much about an economic impact of such major magnitude (to say nothing of the noneconomic effects of curing people ill with formerly fatal diseases).

So more effective therapy is sometimes cheaper, but certainly not always, at least not with today's cancer treatment. The argument that successful research will always, eventually, lead to cheaper treatment may well be true, but at the moment acceptance of this proposition requires a certain leap of faith.

But there are other good arguments as well. It seems obvious that comparative clinical trials are a potentially powerful tool for getting at a cost/benefit analysis of the treatments that are compared. Just as two treatment policies rarely have an identical medical impact on a patient, their economic consequences are often very different. Thus, the insurance industry should care about fostering clinical trials not only because they define relative effectiveness but also because the results of most of them have economic implications. If two treatments are little different in efficacy or toxicity, the economic implications might be a powerful influence on reimbursement decision-making. Clearcut inferiority of a treatment compared to an alternative should constitute strong and rational grounds for subsequent denial of coverage.

If all this sounds reasonable, we must then confront a very awkward fact. Except for truth, justice, and societal responsibility, there really is little incentive for any *individual* insurance company to proceed alone along the lines we have outlined. Why should a company do this unless it has fair assurance in advance that a significant loss of business will not result? It would be more productive for us, therefore, to try to convince the entire industry. If the industry were somehow to adopt a uniform policy recognizing the importance of paying for patient care costs of research subjects on valid experimental programs, the problem of different companies' jockeying for positions of competitive advantage on this issue would be neutralized.

The cost of adopting such a position industry-wide would need to be worked out carefully. One would expect, however, that since much of this has been going on for years anyway, the costs have already been largely incorporated into existing rate structures, and so there might well not be very much of an increase at all, at least not immediately. The impact on the whole system of a few very expensive items, such as autologous bone marrow transplantation or adoptive immunotherapy, would require detailed scrutiny.

How would any resulting increase in health care costs be dealt with? Most likely it would be passed along in the form of higher premiums to the companies, corporations, or individuals buying health insurance policies. Businesses could then in turn be expected to pass on at least some of this cost increase to the consumers of its products, so that the cost of a telephone call or a Taurus might be somewhat higher as a result of increased premiums charged to the telephone company or to Ford. Thus, the economic impact of this policy would be diffused over a very broad segment of the population.

If we do not proceed in this fashion, there are perhaps some other viable alternatives. The costs could be paid by a federal agency, in which case the taxpayer would foot the bill. To the extent that the costs are borne by the drug and device manufacturers, then the consumer (and the health insurance industry!) again will pay, this time via price increases for products of these companies. In any case the cost of supporting research is eventually borne by the citizen or consumer. The most equitable way of distributing these costs across the population is a complex question for economic analysts and philosophers. From my own viewpoint, any solution other than having these costs paid through existing reimbursement mechanisms would be extremely disruptive without very careful coordination and planning.

If the insurance industry were to decide that support of responsible research is in its best interest, how should it go about defining "responsible"? Perhaps peer review should be the arbiter: any study that has the approval of a formal peer-review mechanism managed by the sponsor (the NIH, American Cancer Society, pharmaceutical companies, etc) might be eligible. This would cover most cases but would leave out a number of scientifically valid investigations occurring without such sponsorship (for example, single-institution studies of a new agent produced on the premises). The simplest solution is perhaps to require only that the study be approved by an appropriately constituted Institutional Review Board. In addition to being maximally pluralistic, this would permit a certain variability by locale in deciding what constitutes appropriate care. This mechanism also should be capable of weeding out fraudulent treatments.

How might investigators contribute to this process? First of all, if the reimbursement system were contractually based on the effectiveness of treatment for conventional care, the companies would undoubtedly need expert assistance in making policy decisions about what works in the usual classes of clinical situations. Existing data bases like the NCI's Physician Data Query system might well be useful here, but even if it were, its contents might need expansion and interpretation to cover the large number of clinical situations that would naturally arise.

Second, the oncology community would have to intensify its commitment to comparative trials of innovative therapies (particularly the very expensive ones) as early in their development as feasible, so that their effectiveness can be determined. The Cancer Therapy Evaluation Program has had this issue very high on its agenda in relation to autologous bone marrow transplantation over the past 2 years, but it has proved very difficult, for a variety of reasons (some valid, some less so), to create multicenter tests of the dose-response hypothesis implicit in these studies. If we do not come together on the importance of clarifying these kinds of issues quickly, we may rest assured that the insurance companies will make the necessary decisions without our assistance.

SUGGESTIONS

The assertion that we need a healthy clinical research capability will probably meet with broad agreement. The fighting begins over the knotty question of who is responsible for what. Although these issues are not limited to cancer treatment, oncology is particularly threatened because clinical trials are so integral to the fabric of much cancer medicine. Moreover, many of the most promising approaches are very costly and require inpatient care. The problem is formidable and resists easy solutions, but the potential risks of doing nothing—the loss or crippling of a clinical trials capability that has taken three decades to build—are simply too great.

The major tactical question is how to change the policy of a decentralized industry. The Blue Cross/Blue Shield system alone consists of more than 75 separate companies making independent decisions about reimbursement. To these one must add a large number of private carriers, as well as the federal and state programs responsible for Medicare and Medicaid. How does one begin to change the policy of an industry constructed in this way?

The central element in the strategy has to be education. Key individuals and groups outside oncology must be made to see investigative therapy for what it really is. Even most intelligent and educated people are probably unaware of the centrality of clinical trials in the delivery of state-of-the-art care to patients. It is not simply that clinical trials are essential for progress in treatment, though that is certainly their principal justification; it is also that the care on good clinical trials is state-of-the-art.

Our focus should be on the validity of third-party coverage for all cancer treatment trials that have good scientific justification. Some may object to the inclusion of phase I or early phase II trials, since in these cases there may be no information about antitumor activity and even the appropriate dose may not be known. Nonetheless, patients in these studies are receiving a therapeutic approach that, in the judgment of the treating physician and his peers on the local IRB and at the sponsoring organization, is appropriate medical care under the circumstances, even if the probability of benefit appears small.

The key individuals and groups that need this education are those that determine reimbursement policies. The federal government is both a major health insurer and a major purchaser of insurance policies for its own employees. As a provider of insurance, HCFA makes policies that are important in themselves and also are scrutinized carefully as models by insurance companies. As a purchaser of insurance the government, like any other high-volume consumer, has a lot to say about what kind of product it is ultimately offered. The Congress, which has been traditionally very sympathetic to biomedical research, would probably take a very dim view of a widespread *de facto* exclusion from reimbursement of patients who receive their state-of-the-art care on clinical trials. Once given a proper appreciation of the problem, the Congress could take a variety of actions that would go a long way toward resolving the dilemmas we now face.

Aside from government, the major purchasers of insurance in this country are businesses, which buy huge packages for their employee benefits programs. Here as elsewhere, a business will try to keep its outlays as low as possible, and in response to this, the insurance companies will rid their policies of liability for all "inessentials." Constructive pressure can come from labor unions demanding the best possible fringe benefits or from business executives themselves who feel obliged to provide policies covering quality care.

Who should be responsible for the educational effort? The answer is that we all should be. Lectures in various public forums, interviews with the media, articles for the lay press, and educational programs at cancer centers for laymen within their cachement areas are potentially useful ways of emphasizing the benefits of clinical research, as well as the present limitations of the state of the art and the pressing need to move the field further.

The oncology community can do much more with clinical trials in developing formal comparisons of cost/effectiveness or cost/benefit. This is admittedly difficult, since such studies cannot be done casually or on a shoestring and would require collaboration of experts, such as health care economists, who are currently outside the clinical trials mainstream. Funding for such studies is also not plentiful. Although these kinds of research objectives have not been within the traditional purview of NIH, they clearly fall within the mandate of the National Center for Health Services Research and Health Care Technology Assessment. Unfortunately, constraints on funding have limited the Center's role in the evaluation of new technologies and treatments. Certain private foundations with an interest in evaluation of health care policies might have an interest in supporting such studies. Further emphasis in these directions would be the best demonstration that we share the general concern about the cost of medical care and are willing to work on developing intelligent strategies to effect cost containment. Helping insurance companies with difficult decisions in individual cases may also work toward the same goal.

As the oncology community begins to face the looming problems described here, how should its efforts be coordinated and its concerns represented? The directors of the nation's cancer centers and the chairmen of the clinical cooperative groups are in an ideal position to take on a major share of the responsibility. In addition, the American Society of Clinical Oncology (ASCO) is in a good position to move along the necessarily broad front without any categorical restrictions on the kinds of initiatives it may undertake. ASCO might also be a suitable interface between the oncology community and other interested constituencies, such as the American College of Physicians, the American Federation for Clinical Research, the Society of Clinical Trials, and other subspecialty groups.

REFERENCES

1. MEINERT CL. Funding for clinical trials. Controlled Clin Trials 3:165-171, 1982.
2. CHALMERS TC, VAN DEN NOORT S, LOCKSHIN MD, ET AL. Summary of a workshop on the role of third-party payers in clinical trials of new agents. N Engl J Med 309:1334-1336, 1983.
3. BANTA HD. RCTs and the federal government. Controlled Clin Trials 3:173-183, 1982.
4. WEISS GB. Who pays for clinical research? Clin Res 27:297-299, 1979.
5. LIND SE. Can patients be asked to pay for experimental treatment? Clin Res 32:393-398, 1984.
6. KAHN CR. A proposed new role for the insurance industry in biomedical research funding. N Engl J Med 310:257-258, 1984.

EDITORIAL

Hammering Away at Solid Tumors[1,2]

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Someone (we don't know who) once said that if all you have is a hammer, everything starts to look like a nail. The "hammer" of high-dose chemotherapy or chemoradiotherapy with marrow transplantation, applied so successfully in the treatment of hematologic malignancies, has also been studied as treatment for common solid tumors. Phase I dose escalation studies have defined the maximum tolerable dose of several chemotherapeutic agents administered with marrow support including cyclophosphamide, etoposide, mitomycin, melphalan, thiotepa, and carmustine (BCNU). Phase II studies have defined the response rates of several solid tumors treated with maximum doses of these single agents.

In their study in this issue of *Cancer Treatment Reports*, Antman et al (1) have gone the next step by constructing a drug combination, escalating doses to the maximum tolerated, and measuring responses in a variety of tumors. The specific drug combination (cyclophosphamide, BCNU, and cisplatin) was chosen because of animal studies demonstrating that alkylating agents exhibit sometimes steep dose-response curves and are often non-cross-resistant. Further, each drug has a different dose-limiting nonhematopoietic toxic effect. Thus, the approach taken by these investigators follows what we often think of as the principles of dose-response and of combination chemotherapy.

What have we learned from their study so far? Although the number of patients is small, as far as disease response is concerned, it appears that the response rates, although of short duration, are higher than those achieved with conventional dose therapy. It is, however, less certain that this combination of alkylators given at high dose provides more responses than high-dose single agents. The only two diseases with enough patients to consider in Antman's study are melanoma and breast cancer (the response rates cited here consider all patients treated and we have not "censored" the early deaths). The complete and overall response rates for melanoma in this study were 5% and 55%, respectively, not different from what has been reported with high-dose single-agent BCNU (complete response rate, 16%; overall response rate, 45%) or with high-dose single-agent melphalan (complete response rate, 21%; overall response rate, 74%) (2-4). In Antman's study, the complete and overall response rates for breast cancer are 32% and 79%, which is impressive, but there are few high-dose single-agent data for comparison.

Why didn't the combined alkylator approach give clearly higher response rates than single-agent therapy? One possibility is that combining alkylators is a bad bet even if animal models show non-cross-resistance. Studies by Herzig et al (5) in melanoma suggest that the combination of high-dose BCNU and high-dose melphalan gives no more responses than either agent alone. In a recent Southwest Oncology Group study, combined alkylators for extensive small cell lung cancer failed to demonstrate an advantage over a standard cyclophosphamide, doxorubicin, and vincristine regimen (6).

A second possible reason for the apparent failure of the high-dose alkylator combination is that advanced disease resistant to standard dose therapy is too difficult and that if tested in more sensitive tumors or earlier in the disease course, additive or synergistic activity will be seen. For example, the combination of busulfan and cyclophosphamide is clearly more active than cyclophosphamide alone for acute nonlymphocytic leukemia (single-agent busulfan has not been extensively evaluated) (7).

These possible reasons for failure suggest two future approaches. One approach is to explore other combinations, a formidable task considering the number of drugs, drug combinations, and relative dose relationships possible (eg, should the cyclophosphamide:BCNU ratio always be 10:1 as in the Antman study or are there other better ratios?).

Another direction is to apply these regimens earlier in the disease course and in more drug-sensitive tumors. Maybe a 50% response rate in melanoma, even if for a median of only 4 months, is enough to translate into more cures if applied in the adjuvant setting. After all, in the two diseases where adjuvant chemotherapy is most clearly of use (breast cancer and osteogenic sarcoma), the overall response rates for patients with metastatic disease to the adjuvant regimens (cyclophospha-

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mide, methotrexate, and 5-fluorouracil for breast cancer and high-dose methotrexate for osteogenic sarcoma) are ≤ 50%. However, the toxic effects of these standard adjuvant chemotherapy regimens are considerably less than those seen in Antman's study, which resulted in 15% of the patients dying as a direct result of treatment. To study the sort of very aggressive regimen described by Antman early in a patient's disease requires careful identification of a patient population with a very low chance of cure with conventional approaches.

Curiously, some of the patients in Antman's study died of toxic effects not seen with any of the individual agents, particularly hypertension, platelet consumption, and a virulent form of veno-occlusive disease of the liver. Thus, while it is unclear that combining alkylating agents was additive or synergistic for tumor response, it seemed to be so for toxicity. Neither the mechanisms of these toxic effects nor the reasons for individual patient sensitivities are known. Unexpected toxic effects have been seen with other high-dose combinations such as the acute cardiomyopathy we saw with the BCNU, cytarabine, cyclophosphamide, and 6-thioguanine regimen, a toxic effect which on the basis of electron microscopy we felt was due to direct endothelial damage (8). Antman et al (1) suggest a similar mechanism for their toxic effects, which seems plausible enough, but why different target organs and what puts a patient at risk? Clearly, a great deal of preclinical work in understanding mechanisms of drug toxicity is needed.

Future clinical studies of high-dose regimens need to clearly define the toxic effects directly associated with treatment as Antman has done. A problem here is the lack of a grading system which discriminates toxic effects at the high end of the scale. For example, the current Southwest Oncology Group's toxicity scale has as grade 3 liver toxicity (the highest grade) a bilirubin ≥ 5 mg/100 ml. For transplant purposes, a bilirubin of 10 mg/100 ml may be acceptable if transient and completely reversible in all patients. We have been using the grading system shown in table 1 and have found it useful for evaluating toxic effects directly related to the treatment regimen while carrying out dose-finding studies in preparation for marrow transplantation. This grading system was, in fact, derived in part from a system used by Antman et al (1) for their studies. Using this system we found that the standard regimen of cyclophosphamide and 1200 rad of total-body irradiation results in a 10% incidence of severe (grade 3 or 4) toxicity.

The regimen detailed by Antman et al (1) is quite toxic and the responses were of short duration. There

TABLE 1.—Toxicity grading scale for transplant preparative regimen-related toxicity*

	Grade				
Toxic effect	0	1	2	3	4
CNS	None	Transient somnolence	Somnolence > 36 hrs or other signs of CNS toxicity	Seizures Coma	Fatal toxicity
Hepatic	None	Increase in liver function tests	Increase in bilirubin to ≥ 5 × normal Increase in SGOT to ≥ 5 × normal Ascites	Hepatic failure Hepatorenal syndrome Hepatic encephalopathy	Fatal toxicity
Pulmonary	None	Decrease in pO_2 or dyspnea without an infiltrate	Transient interstitial pneumonia not requiring ventilatory support	Interstitial pneumonia requiring ventilatory support	Fatal toxicity
Renal	None	Increase in serum creatinine to 2 × normal	Increase in serum creatinine to > 2 × normal not requiring dialysis	Dialysis required	Fatal toxicity
Gastrointestinal					
Mucositis	None	Pain or ulceration not prohibiting oral intake	Painful ulceration prohibiting oral intake	Severe ulceration requiring intubation	Fatal toxicity
Diarrhea	None	Watery stools < 3 L/day or 6 stools/day	Watery stools > 3 L/day or 6–12 stools/day Hemorrhagic colitis not requiring transfusions	Hemorrhagic colitis requiring transfusions or ileus requiring nasogastric suction	Fatal toxicity
Cardiac	None	Cardiomegaly without symptoms ECG change not requiring treatment	ECG change or congestive heart failure requiring treatment	Congestive heart failure or severe arrhythmia unresponsive to treatment	Fatal toxicity
Skin	None	< 50% of body surface	> 50% of body surface	Generalized desquamation Bulla formation	Fatal toxicity

*When applying this grading scale, only toxic effects directly related to the preparative regimen should be considered. Toxic effects due to graft-versus-host disease or infection are not considered to be regimen-related.

are no data to suggest that patients treated with this approach lived longer than they would have if treated with standard dose therapy or no therapy at all. But saying all this does not mean this study was a failure. The goals as stated by the authors were to define the maximum tolerated dose of their drug combination and to determine the response rates in a variety of solid tumors. They have achieved their first goal, and for breast cancer and melanoma have gone a reasonable distance towards the second. The authors suggest in their last paragraph that they are not satisfied with their current regimen and are looking at alternatives which they hope to apply earlier in the disease course of some patients. This promises to be a difficult task for all the reasons stated and one additional one—who will pay? Research grants virtually never provide much in the way of funding for hospital care and many insurance companies won't cover this "experimental therapy" (9). Some patients may be willing to pay themselves, but this will cut accrual rates and introduce a large patient selection bias.

Certainly, we are all waiting for less toxic, more effective, and more intellectually satisfying anticancer therapies. But we have been waiting a long time. The use of intensive therapy with autologous transplantation has led to *cures* in several otherwise incurable diseases (malignant lymphoma and neuroblastoma) and has led to increased response rates in other malignant diseases. Therefore, though the progress is slow and difficult, it is reasonable for some of us to keep hammering away.

REFERENCES

1. ANTMAN K, EDER JP, ELIAS A, ET AL. High-dose combination alkylating agent preparative regimen with autologous bone marrow support: the Dana-Farber Cancer Institute/Beth Israel Hospital Experience. Cancer Treat Rep 71:119–125, 1987.
2. PHILLIPS GL, FAY JW, HERZIG GP, ET AL. Intensive 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), NSC-4366650 and cryopreserved autologous marrow transplantation for refractory cancer: a phase I–II study. Cancer 52:1792–1802, 1983.
3. LAZARUS HM, HERZIG RH, GRAHAM-POLE J, ET AL. Intensive melphalan chemotherapy and cryopreserved autologous bone marrow transplantation for the treatment of refractory cancer. J Clin Oncol 1:359–367, 1983.
4. APPELBAUM FR, and BUCKNER CD. Overview of the clinical relevance of autologous bone marrow transplantation. *In* Clinics in Haematology. Autologous Bone Marrow Transplantation. London, W. B. Saunders Co, 1986, pp 1–18.
5. HERZIG RH, PHILLIPS GL, LAZARUS HM, ET AL. Intensive chemotherapy and autologous bone marrow transplantation for the treatment of refractory malignancies. *In* Autologous Bone Marrow Transplantation. Houston, University of Texas, 1985, pp 197–202.
6. LIVINGSTON RB, SCHULMAN S, MIRA JG, ET AL. Combined alkylators and multiple-site irradiation for extensive small cell lung cancer: a Southwest Oncology Group study. Cancer Treat Rep 70:1395–1401, 1986.
7. SANTOS GW, TUTSCHKA PJ, BROOKMEYER R, ET AL. Marrow transplantation for acute nonlymphocytic leukemia after treatment with busulfan and cyclophosphamide. N Engl J Med 309:1347–1353, 1983.
8. APPELBAUM FR, STRAUCHEN JA, and GRAW RG. Acute lethal carditis caused by high-dose combination chemotherapy: a unique clinical and pathological entity. Lancet 1:58–62, 1976.
9. VAUGHAN WP, PURTILO RB, BUTLER CD, ET AL. Ethical and financial issues in autologous marrow transplantation: a symposium sponsored by the University of Nebraska Medical Center. Ann Intern Med 105:134–135, 1986.

High-Dose Combination Alkylating Agent Preparative Regimen With Autologous Bone Marrow Support: The Dana-Farber Cancer Institute/Beth Israel Hospital Experience[1,2]

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Fifty-nine patients received 61 courses of cyclophosphamide, cisplatin, and carmustine combined. The phase I study consisted of seven dose escalations. Dose levels 5 and 6 also included the attempted addition of melphalan at 40 and 80 mg/m^2. The maximum tolerated dose for the three-drug combination was 5620 mg/m^2 of cyclophosphamide, 165 mg/m^2 of cisplatin, and 600 mg/m^2 of carmustine. The dose-limiting toxic effect was fatal veno-occlusive disease of the liver in two of five patients treated at the highest dose level. Veno-occlusive disease of the liver was fatal in two of 40 patients treated at Dose level 4, the maximum tolerated dose. The median time to recovery of polymorphonuclear leukocyte counts to $> 500/\mu l$ and platelet counts to transfusion independence $> 20{,}000/\mu l$ was 19 and 22 days, respectively, after marrow reinfusion. Other toxic effects observed included postdischarge pulmonary toxicity, which appeared to respond to prednisone therapy. Thus, this combination of alkylating agents can be combined at close to the transplant dose of each individual agent. The response rate was high despite considerable prior treatment in most patients. Of 16 evaluable patients with breast cancer, 15 responded (six complete responses). Of six evaluable patients with sarcoma, six responded (one complete response). While patients with melanoma had had no prior treatment, 11 of 17 patients responded (65%). There are currently three patients who are disease-free. Two patients with melanoma were rendered disease-free by excisional biopsy of the only remaining nodule after good partial response, and a patient with metastatic breast cancer remains disease-free after a complete response at 36+ months. [Cancer Treat Rep 71:119–125, 1987]

While combination chemotherapy at standard doses is curative in half of the patients with untreated Stage IV Hodgkin's disease and large cell lymphoma, < 10% of the patients with small cell lung cancer or Stage III or IV ovarian cancer survive disease-free after conventional combination chemotherapy. Although responsive to a number of agents, metastatic breast cancer has not been curable. Other common tumors, such as melanoma, are even less sensitive to current standard chemotherapy.

Preliminary data suggest that high-dose chemotherapy with or without total-body radiotherapy followed by autologous bone marrow transplantation (ABMT) may be curative in relapsed Hodgkin's disease and in non-Hodgkin's lymphoma (1–3) and may increase the percentage of long-term disease-free survivors in small cell carcinoma of the lung (4,5). The experience with ABMT in other common adult solid tumors (such as breast, ovarian, and non-small cell lung cancers and sarcoma) is limited.

The major limitation in the use of ABMT in the majority of adult solid tumors is the lack of an effective tumor ablative preparative regimen. Thus, an important aspect for further study is the rational design and systematic evaluation of effective preparative regimens for common solid tumors. Alkylating agents as a group possess properties that make them attractive in the design of such regimens. Alkylating agents exhibit steep dose-response curves (6,7), non-cross-resistance (8,9),

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therapeutic synergy (10), broad clinical activity in a variety of human tumors, and varying nonmyelosuppressive dose-limiting toxicity. Although exceptions exist (eg, etoposide and cytarabine), other classes of cytotoxic chemotherapy have dose-limiting organ toxicity (eg, cardiotoxicity for doxorubicin), which precludes significant dose escalation.

Based on these characteristics of alkylating agents, we have designed a combination alkylating agent regimen consisting of cyclophosphamide, cisplatin, carmustine (BCNU), and melphalan with ABMT support. The phase I dose escalation portion of this study (29 patients) has been previously reported (11). Herein we report the phase I and II data for a total of 61 courses.

METHODS

Patients with unresectable or metastatic malignancies referred for consideration of STAMP (solid tumor autologous marrow program) therapy were initially evaluated via history, physical examination, histopathologic review, renal and hepatic chemistries, creatinine clearance, ECG, chest roentgenogram, pulmonary function tests, computerized tomography (CT) of the head, and bilateral posterior iliac crest bone marrow aspirations and biopsies. Physiologic age > 55 years; CNS or bone marrow metastases; or any significant hepatic, renal, or cardiopulmonary impairment rendered a patient ineligible. Prior chemotherapy excluded patients with melanoma; otherwise, failure of at least one standard regimen was required. (Two previously untreated patients with breast cancer were transplanted with special Human Protection Committee approval. *See* Results section.)

Under general anesthesia, bone marrow was harvested from the posterior iliac crests and was subsequently cryopreserved at −190°C until reinfusion.

Chemotherapy

Patients were admitted to a private room under reverse isolation and allowed a low bacterial content diet. Cisplatin was infused continuously on Days −7 to −5 (table 1), with cyclophosphamide delivered iv over 1 hour on each of the 3 days. BCNU was infused over 2 hours on Day −4 for the first 49 courses and twice a day from Day −7 to Day −4 for the remaining patients. Melphalan was administered on Day −5 for patients on Dose levels 5 and 6 only.

TABLE 1.—Solid tumor autologous marrow program (STAMP I)

	Day from marrow reinfusion								
	−8	−7	−6	−5	−4	−3	−2	−1	0
Bone marrow harvest	X								
Chemotherapy									
Cyclophosphamide		X	X	X					
Cisplatin		X	X	X					
BCNU*					X				
Melphalan†				X					
Bone marrow reinfusion									X

*Given as shown to the first 49 patients. Thereafter, the same total dose was divided and given twice/day over Days −7 to −4.

†Given to 7 patients on Dose levels 5 and 6.

Perphenazine and benadryl were utilized as antiemetics; steroids and barbiturates were excluded because of possible alteration of cyclophosphamide and BCNU pharmacokinetics. During chemotherapy the bladder was irrigated to prevent hemorrhagic cystitis.

Three patients were studied at each phase I dose level. When the combination of cyclophosphamide, cisplatin, and BCNU produced dose-limiting toxicity, the dose of the three drugs was decreased and melphalan was added at two dose levels. Additional patients were accrued at the maximum tolerated dose (MTD) to determine the incidence of nonhematologic toxicity. The phase II study was undertaken to estimate response rates for melanoma, breast cancer, and sarcoma and to pilot the regimen in other common solid tumors.

Bone Marrow Reinfusion and Supportive Care

The bone marrow was thawed 3 days following completion of chemotherapy (Day 0). A median number of 8.3×10^9 nucleated cells was infused per patient. (One patient died before marrow infusion.) One-half to two-thirds of the harvested marrow remained frozen in reserve in the event of poor engraftment. This was used in two patients who had wbc counts $< 100/\mu l$ and no significant engraftment on bone marrow biopsy by Day 18.

All blood products were irradiated (5000 rad). Platelet transfusions, which were HLA-matched when appropriate, were administered when the platelet count fell to $< 20{,}000/\mu l$. Platelet transfusions were either pooled random donor concentrates (six to ten products, 8.3×10^{10} platelets per product, mean count) or single-donor pheresis products containing 4–10 units of platelets (1 unit = 5.5×10^{10} platelets).

When fever developed in a patient with a wbc count $< 1000/\mu l$, empiric broad-spectrum antibiotics were begun with subsequent dose and agent modification based on the sensitivities of any isolated organisms or evident infection.

The extent of disease was established prior to initiation of chemotherapy and tumor size was measured weekly when possible. Complete and partial responses were defined as a 100% and 50%–99% reduction, respectively, in the sum of the products of the perpendicular diameters of all measurable lesions for a minimum of 4 weeks. Patients who died with < 4 weeks of observation were coded as unevaluable despite evidence of response. Disease progression was recorded whenever it occurred, since no "duration" is required.

The associations between toxicity and dose level and between veno-occlusive disease (VOD) of the liver and patient characteristics or dose level were evaluated with a Wilcoxon mid-rank statistic (12). Median survival times and the time to hematologic recovery were estimated using the method of Kaplan and Meier (13). The 95% confidence intervals around the medians were calculated using Greenwood's estimate of the variance (14). Survival was measured from the initiation of chemotherapy to the date of death or date of last follow-up. The time to disease progression among MTD responders was measured from the initiation of chemotherapy to the date of progression and censored if still in response or if a toxic death. Two patients were re-treated in response during dose escalation. The duration of the first response was censored at the beginning of the second treatment and the patient was considered unevaluable for response during the second treatment. Survival of these two patients was measured from the start of the first treatment to death or censor, if alive.

RESULTS

Between March 1983 and December 1985, 59 patients received 61 courses of the combination of cyclophosphamide, cisplatin, and BCNU (table 2). Seven of these patients also received melphalan on Dose levels 5 and 6. The median age was 36 years (range, 20–57). The program by virtue of referral patterns and self-selection included predominantly younger patients. The Cancer and Leukemia Group B performance status was 0 for 38 patients, 1 for 20, and 2 for three. Patients with melanoma had received no prior chemotherapy. Two of the patients with breast cancer had had no prior chemotherapy (after Human Protection Committee approval). The remaining patients had generally failed multiple regimens.

Toxicity

Anesthesia and marrow harvests were uncomplicated. Nausea and vomiting were moderate to severe despite antiemetics during chemotherapy. Short episodes of asystole precipitated by nausea and vomiting in one patient required placement of a temporary transvenous pacemaker for the duration of chemotherapy. When severe, BCNU-associated hypotension and flushing (15) were ameliorated by slowing the BCNU infusion and fluid administration. These symptoms were not observed using the more recent divided dose schedule.

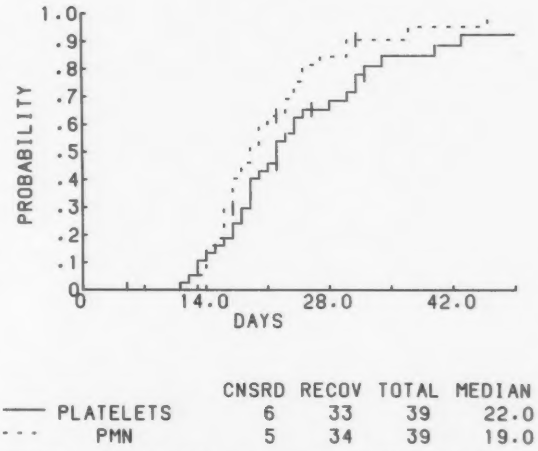

FIGURE 1.—Time to platelet count recovery (> 20,000/μl) and polymorphonuclear leukocyte count (to > 500/μl) for the MTD level 4. 1 patient, who died prior to reinfusion, is omitted from the fig. Censored patients either died early (5 patients) or were recently transplanted and have not yet recovered (1 patient).

Hematologic toxicity.—Myelosuppression was profound (table 2). For Dose level 4 (the MTD), the median time to recovery of polymorphonuclear leukocyte counts > 500/μl and platelet counts to transfusion independence (> 20,000/μl) was 19 and 22 days, respectively, following marrow reinfusion (fig 1). The reserve marrow was administered to two patients who had inadequate wbc and platelet count recovery by Day +18 and no significant recovery on bone marrow biopsy. One patient eventually recovered normal bone marrow function; the second had normal wbc count recovery but chronically low platelet counts. A median of 149 units (range, 39–1500) of platelets was administered per patient course. The platelet count was < 5000/μl for ≥ 2 consecutive days in 13 patients despite as many as six platelet transfusions per day between Day 14 and Day 21. Although antiplatelet antibodies were detected in two patients, the use of HLA-matched platelet products did not increase platelet survival. There were five episodes of thrombocytopenia-associated hemorrhage; three were

TABLE 2.—Myelosuppression by dose level

Dose level	No. of patients	Highest administered dose (mg/m²)				Polymorphonuclear count < 500/μl*	Platelet count < 20,000/μl*
		Cyclophosphamide	Cisplatin	BCNU	Melphalan		
1	3	1500	75	150	0	8 (2-8)	2 (0-10)
2	3	3000	120	300	0	14 (11-15)	11 (8-14)
3	3	3750	150	450	0	24 (12-28)	29 (14-22)
4 (MTD)	40	5625	165	600	0	19 (7-38)	22 (12-50)
5	4	5625	180	600	40	11 (7-22)	26 (21-29)
6	3	5625	180	600	80	13 (8-25)	22 (6-34)
7	5	7500	180	750	0	20 (16-40)	32 (16-44)

*Median No. of days (range).

TABLE 3.—No. of severe and life-threatening toxic effects (deaths) by dose level

	Dose level				
	1–3	4	5–6	7	Total
Total patients treated	9	40	7	5	61
Total deaths	0	6	3	4	13*
Myelosuppression					
Fever > 101°F	7	38 (4)	7 (1)	5	51 (5)
Viral infections					
Herpes simplex during treatment	NT†	13	2	2	17
Herpes zoster after discharge	0	4	2	0	6
CMV				1 (1)	1 (1)
Bleeding	1	2 (1)	0	2 (2)	5 (3)
VOD	0	4 (2)	1	2 (2)	7 (4)
Renal failure	0	6 (2)	3 (2)	2	11 (4)
Pulmonary infiltrates					
Infectious	0	2 (2)	0	1 (1)	2 (2)
Drug toxicity	0	4	1 (1)	0	5 (1)
Gastrointestinal					
Diarrhea > 1 L/day	0	17	4	3	24
Severe mucositis	0	1	6	0	7

*Each death had multiple causes.
†NT = not tested.

fatal (one at the MTD). Both fatal CNS hemorrhages occurred in previously untreated patients with melanoma.

Infection.—One patient died of *Escherichia coli* sepsis prior to marrow reinfusion (table 3). All but two of the remaining patients developed fever (> 101°F) during the period of profound myelosuppression (table 3). Five patients, all with extensive prior therapy, died of sepsis and one previously untreated patient with melanoma died of cytomegalovirus (CMV) pneumonia. Herpes zoster requiring acyclovir developed 3–5 months following therapy in six patients.

Hepatic toxicity.—Early transient SGOT elevations to 30 Wacker units (normal, 8–26 units/ml) were observed in 85% of treatment courses, with return to normal by Day 6 in all but three patients (one who was discharged on Day 10 with an elevated SGOT and two who died of nonhepatic causes on Days −2 and +14, respectively). The incidence of early rise in SGOT did not correlate with increasing dose. VOD developed in seven patients (11%) and was characterized by right upper quadrant pain, hepatomegaly, ascites, and jaundice. At autopsy, diagnostic concentric subendothelial thickening and narrowing of the hepatic venule lumen by either reticular fibers or collagen were observed in the four patients who died with VOD. Three of these patients had a premortem diagnosis of VOD and one with a prominent elevation of SGOT rather than bilirubin had a premortem diagnosis of hepatitis. The mean bilirubin of the seven patients with VOD first rose to > 2.0 mg/100 ml on a median of Day +1 (range, −2 to +35). VOD proved to be fatal in two of five patients treated at Dose level 7 and in two of 40 treated at Dose level 4 (the MTD); VOD was the dose-limiting toxic effect of the phase I trial. There was a significant positive correlation of VOD with intensity of prior therapy ($P = 0.041$) and with dose level ($P = 0.03$). Performance status, baseline hematologies, and liver chemistries (which were required to be normal at study entry) were not associated with increased risk. The patients who developed VOD had significantly lower mean platelet counts (40,700 vs $5900/\mu l$; $P = 0.004$, t test) on Day −1.

Renal effects.—All patients had normal renal function on Day −8. Creatinine clearances at Dose level 4 (the MTD) decreased from a median of 147 ml/minute on Day −8 to 83 on Day −1, returning to a median of 89 ml/minute by Day +6. The addition of melphalan (Dose levels 5 and 6) to the therapeutic regimen significantly increased the magnitude ($P = 0.004$) and duration of creatinine elevation ($P = 0.001$) when compared to patients receiving Dose level 7. Thus, melphalan was deleted from the phase II regimen.

Pulmonary toxicity.—Of the three patients who developed infiltrates during the period of aplasia, *E. coli* was the documented infectious organism in one and the second had a pulmonary hemorrhage. The infiltrate in the other patient both developed and subsequently resolved on empiric antibiotics. The results of open lung biopsy in the six patients who developed infiltrates after neutrophil recovery revealed CMV pneumonitis in one patient and were consistent with mild to moderate drug injury or interstitial pneumonitis in the remainder. One of these five patients later died of a pulmonary embolus originating from a Swan-Ganz catheter. The remaining four patients were treated with prednisone; the arterial pO2s returned to normal but the diffusion capacity of carbon monoxide remained abnormal. While steroids were being tapered off, one of these patients, who had relapsed with liver metastases, died of *Pneumocystis carinii* pneumonia. Of 29 asymptomatic patients tested after treatment at Dose levels 4–7, 19 (65%) developed a > 20% decrease in diffusion capacity of carbon monoxide.

Cardiac effects.—Mild volume overload resulting in part from the antidiuretic effect of cyclophosphamide occurred in virtually all patients and was managed by furosemide diuresis. Acute pericardial tamponade requiring a single pericardiocentesis occurred on Day 9 during profound thrombocytopenia in a patient with lung cancer involving the pericardium. Two patients who had had prior doxorubicin developed otherwise unexplained moderate cardiomegaly. Cardiomegaly developed after Day +21, resolved after approximately 6 weeks, and was not associated with any significant pericardial effusion.

Hypertension.—While the median maximum daily diastolic blood pressure (DBP) was 80 mm Hg at the start of therapy on Day −8, DBP > 90 occurred in 85% of the patients despite intensive antihypertensive therapy with nifedepine. Blood pressure returned to normal by discharge, although a few patients required antihypertensive therapy for several weeks at home. The median number of days with a maximum DBP > 90 was 5 (range, 0–42 days). Renin and aldosterone levels in 14 patients and catecholamines in four were unremarkable.

Gastrointestinal effects.—In 24 patients, protracted (> 14 days) sporadic vomiting occurred often with no prior nausea. Diarrhea > 1 L/day was seen in one-third of treatment courses and lasted a median of 1 day. Seven patients developed severe stomatitis or esophagitis. Of these patients, six were those who received melphalan; the seventh had received prior radiotherapy to the nasopharynx. There was a significant association between increasing dose and the incidence of diarrhea ($P = 0.008$) and mucositis ($P = 0.0002$).

Neurological effects.—All patients treated at the MTD were evaluated by admission and discharge audiograms. Seven patients developed moderate to severe high-frequency hearing loss. This did not generally involve lower frequencies including human speech. None of these patients required a hearing aid. One patient, who had had considerable prior vincristine, developed severe distal extremity paresthesias which persisted for 3–4 weeks and remained mild almost 10 months posttransplant.

Antitumor effects.—Response data are summarized in table 4. One patient was lost to follow-up allowing no further x-rays. Three patients were transplanted with no measurable disease. Two patients had measurable disease on CT scan only but died on Days −1 and +5 with no way of evaluating response. Four patients fulfilled size criteria for response but died on Days 8, 20, 25, and 27 without fulfilling duration requirements and therefore were not considered responders. The two remaining patients with minimal response and stable disease at the time of death on Days 21 and 4, respectively, were also considered unevaluable because of short follow-up, since either could have responded or progressed if followed for the requisite period.

Three patients currently remain disease-free 16–36 months after transplant. One previously untreated patient with breast cancer had a complete response of hilar and pleural metastases and is disease-free at 36 months. All patients with breast cancer were premenopausal; all but one were estrogen receptor-negative. Two patients had had no prior chemotherapy and two had had prior adjuvant chemotherapy only. Twelve of the remaining patients had less than a partial response to initial chemotherapy or disease progression while receiving adjuvant chemotherapy. Of 16 patients treated with a second regimen, 13 initially progressed. Seven patients had had three prior agents; five patients, four; and five patients, five or more.

Melanoma patients had received no prior chemotherapy. Two partial responders with melanoma subsequently underwent excisional biopsy of their sole remain-

TABLE 4.—Response by dose level and disease

	No. of patients	Response*				% RR/E†	Mos to disease progression	
		UE	NR	PR	CR		Median‡	Range
Dose level								
1–3	9	1	2	6	0	75	3.9	1–4.9
4 (MTD)	40	6	9	19	6	74	4.7	1–35+
5–6 (melphalan)	7	3	0	3	1	100	—	1.9–4.7
7	5	2	0	1	2	100	—	1.8+-3.2
	61	12	11	29	9	78		
Disease								
Breast cancer	19	3	1	9	6	94	3.2	1–35+
Melanoma	20	3	6	10	1	65	4.7	1–23+
Sarcoma	8	2	0	5	1	100	3.9	1.8–6.8
Non-small cell lung cancer	4	2	1	1	0	50	—	3.5
Lymphoma	3	0	1	1	1	67	—	2.9, 10.3
Ovarian cancer	2	0	0	2	0	100	—	3.8, 4.3
Colon cancer	2	0	2	0	0	0	—	—
Testis cancer	1	1	0	0	0	—	—	—
Small cell lung cancer	1	1	0	0	0	—	—	—
Nasopharyngeal cancer	1	0	0	1	0	—	—	2
Total	61	12	11	29	9			

*UE = unevaluable (< 4 wks observation); NR = no response (< 50% response); PR = partial response (50%–99% response); and CR = complete response (100% response).

†RR = response rate (% PR + CR), and E = evaluable patients.

‡Calculated by life-table (Kaplan-Meier) method. Cases censored if: continuing response (3 patients), toxic death while in response (5 patients), at time of second STAMP while in response (2 patients), non-STAMP-related surgical death (1 patient), or CNS metastases despite continued peripheral response (1 patient).

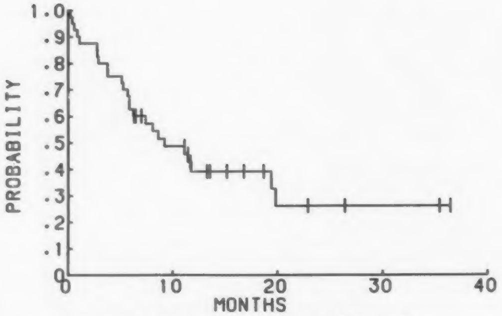

FIGURE 2.—Survival of patients treated at the MTD level.

ing measurable nodule and remain disease-free at 16 and 23 months. In addition, a young woman with rapidly progressing melanoma experienced an 11-month period of stable disease.

Of the 40 patients treated at the MTD, the median times to disease progression among responders and survival are 4.7 and 9.3 months, respectively (figs 2 and 3).

DISCUSSION

Cyclophosphamide, cisplatin, and BCNU, which have had differing nonmyelosuppressive toxic effects when individually dose-escalated with ABMT, can be combined at nearly the MTD for each individual agent (16–23). However, the addition of relatively low doses of melphalan to the high-dose combination of cyclophosphamide, BCNU, and cisplatin created unacceptable gastrointestinal and renal toxicity.

Excessive platelet consumption occurred in 13 patients. Despite administration of as many as 50 units of platelets/day on Days 7–21, the platelet count remained $< 5000/\mu l$ for > 2 consecutive days in each of these patients. HLA-compatible products did not significantly improve platelet survival. The etiology of this rapid platelet consumption is not understood. Laboratory evidence of an acquired abnormality of von Willebrand's factor multimer distribution was found in some of these patients (24). Alkylating agent-induced endothelial damage might also result in these observed phenomena. Endothelial damage has also been postulated as the mechanism by which other alkylating agents have been associated with the development of Raynaud's phenomenon (25) and microangiopathic hemolytic anemia (26).

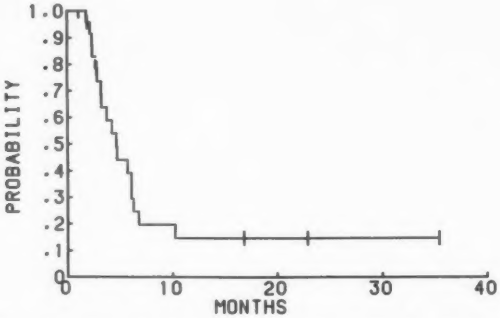

FIGURE 3.—Time to disease progression among responders treated at the MTD level. Censored patients indicated by the tic marks have not yet progressed.

It was not the intent of this trial to determine whether bone marrow would eventually recover after treatment with these doses. The fact that the reserve marrow was used in two patients suggests that marrow recovery would have been slow and unpredictable. Certainly, additional delay in marrow recovery without ABMT would have resulted in additional toxic deaths.

VOD was the second most common cause of treatment-related death in this series (after infection). Reports from other centers also document a 10%–20% incidence of VOD in patients undergoing transplantation for malignancy (27,28). Efforts were made to decrease the incidence of this toxicity by changing the drug schedule of BCNU without changing the dose; VOD has not been observed in the 12 patients treated with the divided dose schedule of BCNU (95% confidence interval, 0%–26%).

Significant hypertension developed in 85% of the patients. This rare complication of intra-arterial cisplatin therapy (29) may be another manifestation of endothelial damage. The moderate cardiomegaly which developed in two patients developed later than the highly lethal myopericarditis associated with high-dose cyclophosphamide therapy (30,31). A pericardial effusion was not a prominent finding in either patient.

The frequency of objective responses to this three-drug combination was high despite large tumor volumes and documented resistance to standard therapy in most patients (table 4), although patients with melanoma had had no prior chemotherapy. The median duration of unmaintained response and survival is 4.7 and 9.2 months, respectively. Of five partial responders rendered disease-free by further resection and radiotherapy after ABMT, two are disease-free at 16 and 23 months. In addition, a breast cancer patient with a complete response remains disease-free at 36 months.

The toxicity of this regimen, however, is also formidable, with a 15% mortality at the MTD. Three of the six total deaths at the MTD occurred in the four patients with VOD. While mortality from bacterial sepsis was confined to patients with extensive prior treatment, both episodes of CNS hemorrhage (two of three episodes of lethal bleeding) developed in previously untreated melanoma patients. A proclivity for CNS bleeding in melanoma patients, even without evident CNS metastases by CT scan, has been observed by others (32).

An acceptable mortality rate for such a transplant regimen depends on the prognosis of the patient population treated and the curative potential of the definitive regimen. Because allogeneic bone marrow transplantation for acute myelocytic leukemia in second remission is known to be curative in ~50% in a population with no significant chance of cure with standard chemotherapy, a high mortality has been acceptable. Conversely, the treatment of an indolent but uniformly fatal disease, such as previously untreated metastatic breast cancer with only a few long-term disease-free survivors, would require a very low mortality. Thus, a 15% mortality rate would be acceptable if a preparative regimen were proven to be curative in a substantial fraction of otherwise incurable patients. Unfortunatelly, during phase I and II testing in patients with extensive prior treatment and advanced disease, the eventual efficacy and toxicity of a regimen in the targeted good-risk population without extensive prior treatment are unknown. It is reasonable to expect that variations in the regimen and modification in supportive care could substantially decrease the early mortality when such a curative regimen is identified. In addition, a lower mortality rate would be expected in a less extensively treated population.

We are currently investigating variations of this regimen in an attempt to increase the efficacy and decrease the morbidity and mortality of the regimen. A modification of the regimen reported here is being used in patients with small cell lung cancer who are currently responding to a standard induction regimen. A regimen of high-dose cyclophosphamide, thiotepa, and melphalan is being tested for patients with breast cancer.

REFERENCES

1. ANDERSON KC, and NADLER LM. Autologous bone marrow transplantation in the therapy of lymphomas. *In* Important Advances in Oncology (DeVita VT, Jr, Hellman S, and Rosenberg SA, eds). New York, J. B. Lippincott. In press.
2. ARMITAGE JO, JAGANNATH S, SPITZER G, ET AL. High-dose therapy and autologous marrow rescue as salvage treatment for patients with large cell lymphoma. Manuscript submitted to the Journal of Clinical Oncology.
3. APPELBAUM FR, and THOMAS ED. Review of the use of marrow transplantation in the treatment of non-Hodgkin's lymphoma. J Clin Oncol 1:440-447, 1983.
4. SPITZER G, DICKE K, ZANDER AR, ET AL. High-dose intensification therapy with autologous bone marrow support for limited small-cell bronchogenic carcinoma. J Clin Oncol 4:4-13, 1986.
5. HUMBLET Y, SYMANN M, BOSLY A, ET AL. Late intensification (LI) with autologous bone marrow transplantation (ABMT) for small-cell bronchogenic carcinoma. J Clin Oncol 4:4-13, 1986.
6. FREI E, III, and CANELLOS GP. Dose, a critical factor in cancer chemotherapy. Am J Med 69:585-594, 1980.
7. FREI E, III. Antitumor agents—dose response curve, clinical and experimental consideration. Exp Hematol (suppl 5)7:262-264, 1979.
8. SCHABEL FM. Combination chemotherapy. *In* Cancer Chemotherapy: The Biochemistry (Montgomery J, ed). New York, Marcel Dekker, Inc, 1983, pp 1-69.
9. FREI E, III, CUCCHI C, ROSOWSKY A, ET AL. Alkylating agent resistance: in vitro studies of human cell lines. Proc Natl Acad Sci USA 82:2158-2162, 1985.
10. SCHABEL FM. Synergism and antagonism among antitumor agents. *In* The Pharmacologic Basis of Cancer Chemotherapy. Baltimore, MD, Williams and Wilkins Co, 1975, pp 595-623.
11. PETERS WP, EDER JP, HENNER WD, ET AL. High-dose combination alkylating agents with autologous bone marrow support: a phase one trial. J Clin Oncol. In press.
12. MEHTA CR, PATEL NR, and TSIATIS AA. Exact significance testing to establish treatment equivalence with ordered categorical data. Biometrics 40:819-825, 1984.
13. KAPLAN E, and MEIER R. Nonparametric estimation from incomplete observation. J Am Stat Assoc 53:457-481, 1958.
14. COX DR, and OAKES D. Analysis of Survival Data. London, Chapman and Hall.
15. HENNER WD, PETERS WP, EDER JP, ET AL. Pharmacokinetics and immediate effects of high-dose carmustine in man. Cancer Treat Rep 70:877-880, 1986.
16. SPITZER G, DICKE KA, VERMA DS, ET AL. High-dose BCNU therapy with autologous bone marrow infusion: preliminary observations. Cancer Treat Rep 63:1257-1264, 1979.
17. HERZIG GP, PHILLIPS GL, HERZIG RH, ET AL. High-dose nitrosourea (BCNU) and autologous bone marrow transplantation: a phase I trial. *In* Nitrosoureas, Current Status and New Developments (Prestayko AW, Crooke ST, Baker LH, et al, eds). New York, Academic Press, 1981, pp 337-341.
18. PHILLIPS GL, FAY JW, HERZIG GP, ET AL. Phase I-II study: intensive BCNU (1,3-bis) 2-chloroethyl-1-nitrosourea, carmustine, NSC-409962 and autologous bone marrow transplantation for refractory cancer. Cancer 52:1792-1802, 1983.
19. TAKVORIAN T, PARKER LM, HOCKBERG FH, ET AL. Autologous bone marrow transplantation: host effects of high dose BCNU. J Clin Oncol 1:610, 1983.
20. LAZARUS HM, HERZIG RH, GRAHAM-POLE J, ET AL. Intensive melphalan chemotherapy in cryopreserved autologous bone marrow transplantation for the treatment of refractory cancer. J Clin Oncol 1:359-367, 1983.
21. MCELWAIN TJ, HEDLEY DW, BURTON G, ET AL. Marrow transplantation accelerates hematologic recovery in patients with malignant melanoma treated with high dose melphalan. Br J Cancer 40:72-80, 1979.
22. MCELWAIN TJ, HEDLEY DW, GORDON MY, ET AL. High-dose melphalan in non-cryopreserved autologous bone marrow treatment of malignant melanoma and neuroblastoma. Exp Hematol (suppl)7: 360-371, 1979.
23. HEDLEY DW, MILLER JL, MCELWAIN TJ, ET AL. Acceleration of bone marrow recovery by pretreatment with cyclolphosphamide in patients receiving high dose melphalan. Lancet 2:966-967, 1978.
24. EDER JP, WEINSTEIN MJ, PETERS WP, ET AL. Changes in von Willebrands factor (vWF) in high dose chemotherapy. Proc ASCO 4:268, 1985.
25. VOGELZANG NJ, BOSL GJ, JOHNSON K, ET AL. Raynaud's phenomenon: a common toxicity after combination chemotherapy for testicular cancer. Ann Intern Med 95:288-292, 1981.
26. GULATI SC, SORDILLO P, KEMPIN S, ET AL. Microangiopathic hemolytic anemia observed after treatment of epidermoid carcinoma with mitomycin C and 5-fluorouracil. Cancer 45:2252-2257, 1980.
27. MCDONALD G, SHARMA P, MATTHEWS D, ET AL. Venoocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. Hepatology 4:116-122, 1984.
28. SHULMAN HM, MCDONALD GB, MATTHEWS D, ET AL. An analysis of hepatic venoocclusive disease and centrilobular hepatic degeneration following bone marrow transplantation. Gastroenterology 79:1178-1191, 1980.
29. KLETZEL M, and JAFFE N. Systemic hypertension: a complication of intra-arterial *cis*-diamminodichloroplatinum(II) infusion. Cancer 47:245-247, 1981.
30. APPELBAUM FR, STRAUCHEN JA, GRAW RG, ET AL. Acute lethal carditis caused by high dose combination chemotherapy: a unique clinical and pathologic indice. Lancet 1:58-62, 1976.
31. GOTTDIENER JS, APPLEBAUM FR, FERRANS VJ, ET AL. Cardiotoxicity associated with high dose cyclophosphamide therapy. Arch Intern Med 141:758-763, 1981.
32. LAZARUS HM, HERZIG RH, WOLFF SN, ET AL. Treatment of metastatic malignant melanoma with intensive melphalan and autologous bone marrow transplantation. Cancer Treat Rep 69:473-477, 1985.

Ifosfamide-Induced Subclinical Tubular Nephrotoxicity Despite Mesna[1,2]

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We monitored acute tubular damage in 16 patients who received a 5-day course of ifosfamide (1.6 g/m^2/day) and mesna (1.2 g/m^2/day) therapy. Urinary concentrations of alanine aminopeptidase, *N*-acetyl-β-D-glucosaminidase, and total protein increased in every patient, but the extent of tubular toxicity varied widely among patients. Evidence of toxicity was greatest in patients whose tumors involved the kidneys. The time course of enzymuria and proteinuria indicated tubular cell necrosis. We observed this acute toxic effect despite the administration of sufficient mesna to prevent hemorrhagic cystitis. Urinary marker concentrations returned towards pre-dose levels, and there were no increases in serum creatinine concentrations measured 3 weeks after treatment. [Cancer Treat Rep 71:127-130, 1987]

Ifosfamide therapy is active against many solid tumors, even when patients have not responded to the closely related oxazaphosphorine, cyclophosphamide (1-3). Bladder, renal, and hematopoietic toxicity has limited the dose of ifosfamide that can be administered (1,4,5). Hemorrhagic cystitis is attributed to acrolein, a metabolite of ifosfamide (6,7). By use of compounds possessing free sulfhydryl groups, such as mesna (2-mercaptoethane sulfonate sodium), acrolein can be chemically neutralized and high doses of ifosfamide administered with minimal bladder toxicity (1,8,9). Although the administration of mesna or other sulfhydryl compounds also ameliorates ifosfamide-induced nephrotoxicity (9), renal impairment remains a potential hazard of ifosfamide therapy (10-13).

Conceivably, ifosfamide is subclinically nephrotoxic in all patients, and variable susceptibility to tubular damage predisposes occasional patients to develop clinical toxic effects. To test this hypothesis, we have evaluated subclinical nephrotoxicity in children receiving their first course of ifosfamide, by monitoring the urinary excretion of alanine aminopeptidase (AAP) and *N*-acetyl-β-D-glucosaminidase (NAG), enzymes localized within the brush border and lysosomes of proximal renal tubular cells (14). Urinary total protein concentrations were also measured to detect protein exudate from denuded tubular epithelium and low-molecular-mass serum proteins not reabsorbed by dysfunctional tubular cells (15). We demonstrate ifosfamide-induced subclinical renal damage despite the concurrent administration of mesna.

METHODS

We studied a subgroup of patients enrolled in a phase II investigational trial of ifosfamide (3) who had not received prior cisplatin therapy. Ifosfamide, 1.6 g/m^2, was administered iv over 15 minutes, followed by infusions of mesna, 400 mg/m^2, over 15 minutes at 15 minutes, 4 hours, and 6 hours after ifosfamide. Each course consisted of five daily doses of ifosfamide, for a total of 8 g/m^2. Cisplatin-treated patients were excluded because of the potential for cumulative renal tubular damage that enhances the nephrotoxicity of other drugs (16,17). None of the patients received aminoglycosides or other antineoplastic agents during the period of the study.

Daily urine specimens were obtained during the 5 days of ifosfamide therapy and were stored at 4°C; amorphous salts were removed by centrifugation prior to analysis. Specimens were obtained for 10 days from two patients who agreed to continue urine collections after discharge from the hospital; these specimens were used to identify the temporal pattern of excretion of the urinary markers. Specimens were screened qualitatively by dipstick analysis (Boerhinger-Mannheim Diagnostics, Indianapolis IN) for hemoglobinuria, proteinuria, and

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pH. The activities of NAG and AAP in the urine specimens were determined by modifications of spectrophotometric methods (18,19) for automated determinations by a Micro-KDA analyzer (American Monitor Corp, Indianapolis, IN). Urinary total protein was measured with Coomassie brilliant blue from Bio-Rad Labs, Anaheim, CA. To adjust for variations in urine output, the measured levels of enzyme and protein were expressed relative to the urine creatinine concentration. Serum creatinine concentrations were measured in specimens obtained before and 3 weeks after therapy.

RESULTS

The clinical features of the 16 patients are summarized in table 1. All patients had pretreatment serum creatinine concentrations $\leq$ 1.0 mg/dl. Pretreatment urinary NAG levels exceeded 1.5 U/mmol of creatinine in four children whose tumors involved the kidneys and in another child who had received aminoglycosides during the week before ifosfamide therapy. Postmortem histologic studies, available for three patients who died 3-5 weeks after ifosfamide therapy, disclosed degenerative renal tubular changes; one of these patients had also received a single dose of iproplatin after ifosfamide therapy.

The temporal patterns of enzyme excretion (fig 1) showed that AAP achieved peak concentrations before the fifth day of treatment and that NAG levels were highest between the third and sixth days. Total protein excretion did not peak until the sixth or seventh day.

The acute effect of ifosfamide on excretion of the urinary markers was assessed by comparing the concentration on Day 1 with the maximum concentration achieved during the 5 days of therapy (fig 2). The concentrations of all three markers increased in every patient, albeit to a variable degree. Peak enzyme levels were highest in three children whose tumors involved the kidneys and in the child who had received aminoglycosides immediately prior to ifosfamide therapy.

TABLE 1.—Clinical features of patients

Patient No.	Age (yrs)	Race*	Sex	Diagnosis	Previous therapy†
1	6	W	M	Leiomyosarcoma	C,D,V
2	17	W	M	Osteosarcoma	M
3	20	B	F	Sarcoma	C,D,E
4	13	B	M	Osteosarcoma	C,D,M
5	7	B	F	Rhabdomyosarcoma	A,C,D
6	11	W	F	Osteosarcoma	None
7	5	W	F	Rhabdomyosarcoma	C,D,V
8	8	B	F	Osteosarcoma	D,M
9	9	B	M	Osteosarcoma	A,C,M
10	3	W	M	Fibrosarcoma	D
11	3	W	F	Sarcoma	C,D,E,V
12	20	B	M	Osteosarcoma	A
13	7	W	M	B-cell lymphoma‡	A,C,D,M,V
14	14	B	F	Rhabdomyosarcoma‡	A,C,D,P
15	9	W	F	Rhabdomyosarcoma‡	C,D,U,V
16	6	B	M	Retinoblastoma‡	C,D

*W = white; B = black.

†A = aminoglycosides; C = cyclophosphamide; D = doxorubicin; E = etoposide; M = methotrexate; P = melphalan; U = uninephrectomy; and V = vincristine.

‡Tumor involved the kidneys.

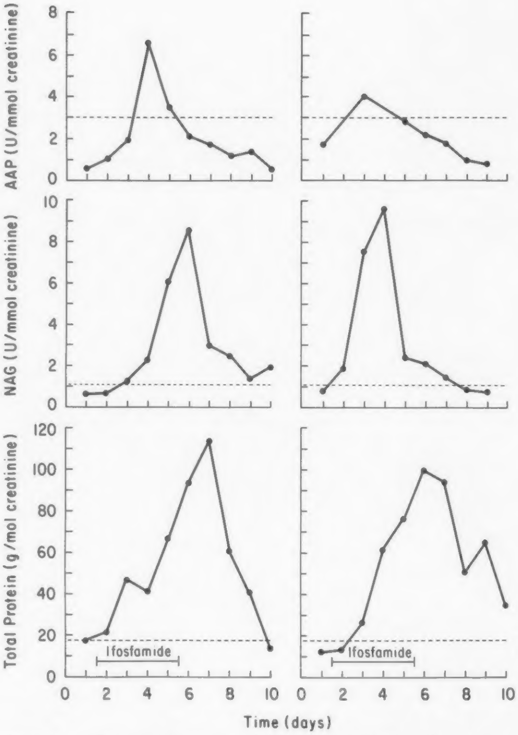

FIGURE 1.—Temporal pattern of urinary AAP, NAG, and total protein excretion in 2 patients (Nos. 3 and 5, table 1) during and after a 5-day course of ifosfamide (1.6 g/m^2/day) and mesna (1.4 g/m^2/day) therapy. Dashed line indicates the upper limit of the normal range.

The enzymuria and proteinuria could not be ascribed to hemorrhagic cystitis. Gross hematuria was not observed in this group of patients. Microhemoglobinuria was detected by dipstick analysis at a $\geq$ 1+ level during seven of the 16 courses. There was no appreciable difference in urinary marker excretion between patients with and patients without microhemoglobinuria.

Serum creatinine concentrations measured 3 weeks after therapy did not differ by $>$ 0.1 mg/dl in comparison to measurements before therapy.

DISCUSSION

Our findings demonstrate ifosfamide-related tubular nephrotoxicity in every patient, despite the concomitant administration of mesna in doses sufficient to prevent hemorrhagic cystitis. The sequence of enzymuria and proteinuria (fig 1) is consistent with ifosfamide-induced necrosis of renal tubular cells. The increase in AAP excretion reflects shedding of the microvilli of tubular

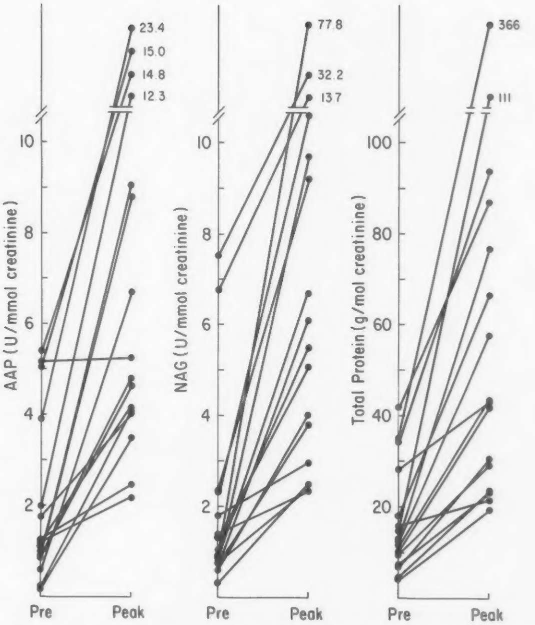

FIGURE 2.—Peak urinary AAP, NAG, and total protein concentrations achieved during 5-day course of ifosfamide and mesna therapy in comparison to preifosfamide values.

cells, whereas the increase in urinary NAG could represent the release of lysosomes into the urine (14). The subsequent proteinuria may be ascribed to sloughing of necrotic cells into the tubular lumen, exudation of protein from the denuded tubular epithelium, and less efficient reabsorption of low-molecular-mass serum proteins in the tubular filtrate (14,15). The observed period of maximal proteinuria coincides with the reported nadir for the creatinine clearance in uninephrectomized adults who received ifosfamide and mesna therapy in a similar schedule (11). These transient declines in creatinine clearance may result from obstruction of renal tubules by cellular casts and reduced secretion of creatinine by dysfunctional or necrotic epithelium.

The acute tubular toxicity can be reversible, as indicated by the normalization of urinary markers following therapy (fig 1) and by the unchanged serum creatinine concentrations measured 3 weeks after ifosfamide treatment. Reports of impaired renal function after ifosfamide therapy (4,5,10–13) may stem from differences in the susceptibility of patients to toxicity (fig 2), especially those whose renal function is compromised by tumor or recent nephrotoxic therapy. After multiple courses of ifosfamide, occasional patients develop a Fanconi syndrome or proximal tubular acidification defect (5,10). In the design of clinical trials to test the efficacy of combination chemotherapy, consideration should be directed towards potential interactions between known tubular nephrotoxins: ifosfamide, cisplatin (16), methotrexate (17), and aminoglycosides (20).

Neither the biochemical mechanism by which ifosfamide damages the kidney nor the means by which mesna ameliorates nephrotoxicity are understood. Acrolein is accepted to be the metabolite of oxazaphosphorines responsible for bladder toxicity (6,7), and evidence suggests that acrolein damages other tissues as well (21,22). Mesna neutralizes acrolein by direct chemical reaction and may protect the urothelial tract by intercepting free urinary acrolein or intracellular acrolein. It seems unlikely that free urinary acrolein would damage only a restricted segment of the renal tubules. Moreover, free urinary acrolein concentrations after oxazaphosphorine administration are estimated to be < 0.5 nmol/ml (23). Hence acrolein produced intracellularly from 4-hydroxyifosfamide, the transport form of the drug, may contribute more to nephrotoxicity than free urinary acrolein. Mesna, which is generated within renal tubular cells by glutathione-mediated reduction of mesna disulfide (24), could detoxify acrolein, chloroacetaldehyde, aldophosphamide and other reactive metabolites of ifosfamide as they are reabsorbed from the urinary filtrate or released intracellularly.

Although adequate for preventing hemorrhagic cystitis, intermittent infusion of the relatively low dose of mesna that we used is not optimal for renal protection. Our estimation of the half-life for elimination of mesna, approximately 30–60 minutes (data not shown), indicates that the urinary concentration is negligible at times when ifosfamide, with reported half-lives ranging from 3 to 15 hours (1,2,25), is still capable of generating toxic metabolites. The apparent protection of the bladder might be ascribed to mesna loading of uroepithelial cells during the periods of high concentration after intermittent infusion. The incidence of ifosfamide nephrotoxicity is reportedly reduced by continuous infusion of mesna (26). Trials to investigate the benefit of larger doses of mesna administered by continuous or intermittent infusion for longer periods of time after ifosfamide are indicated; the subclinical tubular nephrotoxicity of these schedules can be evaluated by use of urinary markers.

REFERENCES

1. BRADE WP, HERDRICH K, and VARINI M. Ifosfamide—pharmacology, safety and therapeutic potential. Cancer Treat Rev 12:1–47, 1985.
2. PINKERTON CR, ROGERS H, JAMES C, ET AL. A phase II study of ifosfamide in children with recurrent solid tumours. Cancer Chemother Pharmacol 15:258–262, 1985.
3. PRATT CB, HOROWITZ ME, MEYER WH, ET AL. Phase II trial of ifosfamide in children with malignant solid tumors. Cancer Treat Rep 71:131–135, 1987.
4. VAN DYK JJ, FALKSON HC, VAN DER MERWE AM, ET AL. Unexpected toxicity in patients treated with iphosphamide. Cancer Res 32:921–924, 1972.
5. DEFRONZO RA, ABELOFF M, BRAINE H, ET AL. Renal dysfunction after treatment with isophosphamide (NSC-109724). Cancer Chemother Rep 58:375–382, 1974.

6. BROCK N, STEKAR J, POHL J, ET AL. Acrolein, the causative factor of urotoxic side-effects of cyclophosphamide, ifosfamide, trofosfamide and sufosfamide. Arzneimittelforschung 29:659–661, 1979.
7. COX PJ. Cyclophosphamide cystitis—identification of acrolein as the causative agent. Biochem Pharmacol 28:2045–2049, 1979.
8. BRYANT BM, JARMAN M, FORD HT, ET AL. Prevention of isophosphamide-induced urothelial toxicity with 2-mercaptoethane sulphonate sodium (mesnum) in patients with advanced carcinoma. Lancet 2:657–659, 1980.
9. FALKSON F, VAN DYK JJ, STAPELBERG R, ET AL. Mesnum as a protector against kidney and bladder toxicity with high-dose ifosfamide treatment. Cancer Chemother Pharmacol 9:81–84, 1982.
10. SANGSTER G, KAYE SB, CALMAN KC, ET AL. Failure of 2-mercaptoethane sulphonate sodium (mesna) to protect against ifosfamide nephrotoxicity. Eur J Cancer Clin Oncol 20:435–436, 1981.
11. FOSSÅ SD, and TALLE K. Treatment of metastatic renal cancer with ifosfamide and mesnum with and without irradiation. Cancer Treat Rep 64:1103–1108, 1980.
12. STUART-HARRIS RC, HARPER PG, PARSONS CA, ET AL. High-dose alkylation therapy using ifosfamide infusion with mesna in the treatment of adult advanced soft-tissue sarcoma. Cancer Chemother Pharmacol 11:69–72, 1983.
13. LOEHRER PJ, SR, WILLIAMS SD, EINHORN LH, ET AL. Ifosfamide: an active drug in the treatment of adenocarcinoma of the pancreas. J Clin Oncol 3:367–372, 1985.
14. PRICE RG. Urinary enzymes, nephrotoxicity and renal disease. Toxicology 23:99–134, 1982.
15. CARONE FA, and GANOTE CE. D-Serine nephrotoxicity. The nature of proteinuria, glucosuria and aminoaciduria in acute tubular necrosis. Arch Pathol 99:658–662, 1972.
16. GOREN MP, WRIGHT RK, and HOROWITZ ME. Cumulative renal tubular damage associated with cisplatin nephrotoxicity. Cancer Chemother Pharmacol 18:69–73, 1986.
17. GOREN MP, WRIGHT RK, HOROWITZ ME, ET AL. Enhancement of methotrexate nephrotoxicity after cisplatin therapy. Cancer 58: 2617–2621, 1986.
18. GOREN MP, WRIGHT RK, and OSBORNE S. Two automated procedures for *N*-acetyl-β-D-glucosaminidase determination evaluated for detection of drug-induced tubular nephrotoxicity. Clin Chem 32: 2052–2055, 1986.
19. JUNG K, and SCHOLZ D. An optimized assay of alanine aminopeptidase activity in urine. Clin Chem 26:1251–1254, 1980.
20. WRIGHT RW, THORNTON D, KALWINKSKY DK, ET AL. Urinary enzyme excretion in children with acute nonlymphocytic leukemia: nephrotoxicity of amphotericin B and aminoglycosides. Clin Chem 31:1013, 1985.
21. BERRIGAN MJ, MARINELLO AJ, PAVELIC Z, ET AL. Protective role of thiols in cyclophosphamide-induced urotoxicity and depression of hepatic drug metabolism. Cancer Res 42:3688–3695, 1982.
22. WILMER JL, EREXSON GL, and KLIGERMAN AD. Attenuation of cytogenetic damage by 2-mercaptoethanesulfonate in cultured human lymphocytes exposed to cyclophosphamide and its reactive metabolites. Cancer Res 46:203–210, 1986.
23. WAGNER T, HEYDRICH D, JORK T, ET AL. Comparative study on human pharmacokinetics of activated ifosfamide and cyclophosphamide by a modified fluorometric test. J Cancer Res Clin Oncol 100:95–104, 1981.
24. ORMSTAD KO, ORRENIUS S, LASTBOM T, ET AL. Pharmacokinetics and metabolism of sodium 2-mercaptoethane-sulfonate in the rat. Cancer Res 43:333–338, 1983.
25. ALLEN LM, CREAVEN PJ, and NELSON RL. Studies on the human pharmacokinetics of isophosphamide (NSC-109724). Cancer Treat Rep 60:451–458, 1976.
26. KLEIN HO, WICKRAMANAYAKE PD, COERPER CL, ET AL. High-dose ifosfamide and mesna as continuous infusion over five days—a phase I/II trial. Cancer Treat Rev 10(suppl A):167–173, 1983.

Phase II Trial of Ifosfamide in Children With Malignant Solid Tumors[1,2,3]

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Ifosfamide was given to 61 patients with malignant solid tumors diagnosed before the age of 21 years. In this phase II study, all patients received 1.6 $g/m^2/day \times 5$ iv over 15 minutes followed by mesna at a dose of 400 mg/m^2 iv at 15 minutes and 4 and 6 hours after ifosfamide. Responses were observed in five of 15 patients with osteosarcoma, two of ten with neuroblastoma, two of six with Wilms' tumor, two of five with rhabdomyosarcoma, four of eight with other soft tissue sarcomas, one of one with retinoblastoma, one of two with germ cell tumors, one of one with B-cell lymphoma, and one of one with a primitive neuroectodermal tumor. Fifty-nine of 61 patients had received prior alkylating agent therapy which included cyclophosphamide, cisplatin, mechlorethamine, melphalan, or dacarbazine. Fourteen of 19 responses developed in patients whose tumors were resistant to treatment with cyclophosphamide. A patient with malignant Schwannoma who had received no prior chemotherapy developed a complete response which lasted 12 months. A patient with brain metastases of osteosarcoma has had complete response for > 2 years. Complete response was also observed in a patient with B-cell lymphoma. Toxicity consisted of mild to moderate nausea and vomiting, transient reversible myelosuppression, occasional elevation of serum BUN or creatinine, and transient neurotoxicity characterized by somnolence, confusion, weakness, tremor, hallucinations, or seizures. We conclude that ifosfamide is an important alkylating agent without apparent complete cross-resistance with cyclophosphamide, and as such should be further investigated for determination of its activity in patients with pediatric neoplasms and considered for incorporation into phase II-III trials for certain tumors. [Cancer Treat Rep 71:131-135, 1987]

Clinical trials testing the activity of ifosfamide were performed during the early 1970s (1-3). Recent descriptions of its activity in adult and childhood soft tissue and bony sarcomas (4-9), as well as germ cell tumors in adult males (10), have generated new interest in this compound. Studies in adults demonstrated that about one-third of the soft tissue sarcomas of these patients responded following ifosfamide, despite prior cyclophosphamide therapy (4-6). Also, one-third of the patients with chemotherapy-resistant metastatic osteosarcoma have achieved responses (7). Complete or partial responses in more than half of a group of children with rhabdomyosarcoma treated with ifosfamide and weekly vincristine have led to the use of this combination as a primary treatment for patients in Europe (5). These encouraging results led us to initiate a phase II trial with ifosfamide in children with malignant solid tumors.

PATIENTS AND METHODS

Sixty-one patients with malignant solid tumors diagnosed before the age of 21 years were entered in this study. Patient characteristics are shown in table 1. Median age of the patients was 11 years 3 months (range, 1 year 10 months to 24 years 6 months).

All patients had histologically confirmed diagnosis of unresectable or metastatic childhood malignant solid tumors and had measurable disease. Fifty-nine of the 61

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TABLE 1.—Patient characteristics

Characteristic	No. of patients
Total	61
Males/females	31/30
Median age in yrs (range): 11.2 (1.9–24.6)	
Prior chemotherapy	59
Prior alkylating agents	59
Cyclophosphamide	39
Cisplatin	41
Melphalan	4
Dacarbazine	4
Mechlorethamine	1
Prior radiation therapy	30
Prior surgery	56

patients had received prior treatment with chemotherapeutic agents. All previously treated patients had received one or more alkylating agents: cyclophosphamide, cisplatin, mechlorethamine, melphalan, or dacarbazine. Median Eastern Cooperative Oncology Group performance status of these patients was 2 (range, 0–3). Additional requirements for entry to the study were normal hemogram and hepatic, renal, and cardiac functions. Informed consent for treatment was obtained from the patient or parent/guardian.

The extent of disease at the time of admission to the study was evaluated with conventional diagnostic imaging studies including radiographs, radionuclide bone scan, abdominal ultrasound, and computed tomography of affected areas. Bone marrow aspirates were obtained from all patients with prior or suspected marrow infiltration by tumor. Hemograms and blood chemistries were performed on Days 1 and 5 of each course and hemograms were obtained weekly between courses of ifosfamide. Daily urinalysis with < 50 rbcs/high-power field was required during each course of treatment.

Ifosfamide was supplied by the Division of Cancer Treatment, National Cancer Institute (Bethesda, MD) and mesna was provided by Asta-Werke A. G. (Bielefeld, Federal Republic of Germany) and by the National Cancer Institute. Ifosfamide [1.6 g/m^2 in sterile water for injection (50 mg/ml)] was infused over 15 minutes for 5 consecutive days. There were no dosage escalations. Mesna (400 mg/m^2) was delivered iv at 15 minutes and 4 and 6 hours after initiation of ifosfamide. Patients received 1000 ml/m^2 of 5% dextrose in one-third normal saline by iv infusion between the 1st and 3rd mesna infusions. During the remainder of the 24 hours patients received 1000–2000 ml/m^2 of fluids orally or by infusion. Antiemetics were delivered as necessary.

Ifosfamide courses were delivered at 21- to 28-day intervals, dependent on recovery of the wbc count to > 2500/mm^3 and the platelet count to $> 100{,}000$/mm^3. Ifosfamide and mesna were withheld in the presence of significant neurologic abnormalities (11) or hematuria (> 50 rbcs/high-power field).

Response was assessed by appropriate diagnostic imaging studies and physical examination after delivery of two 5-day courses of ifosfamide and mesna, unless there was clear evidence of progressive disease. For patients developing complete or partial responses following two treatment courses of ifosfamide and mesna, it was planned to continue these treatments for 12 months, or until there was evidence of progressive disease.

Evidence of nephrotoxicity was sought by the evaluation of the excretion of the urinary enzymes *N*-acetyl-β-D-glucosaminidase and alanine aminopeptidase in urine samples obtained during the treatment courses of 20 patients (28).

Daily electroencephalograms were obtained in 22 patients to assess neurotoxicity of ifosfamide with mesna.

Complete response was defined as the disappearance of all measurable lesions for > 4 weeks. Partial response was defined as a $\geq 50\%$ reduction in the product of the perpendicular diameters of all measurable lesions lasting > 4 weeks. Mixed response was defined as a $> 50\%$ reduction in the product of perpendicular diameters of some measurable lesions but a $< 50\%$ change of other lesions for > 4 weeks. Stable disease was defined as a $< 25\%$ change in measurable lesions. Progressive disease was defined as a $> 25\%$ increase in size of measurable lesions, or the development of new lesions. Duration of response was calculated from the initiation of chemotherapy to the documentation of disease progression.

RESULTS

Of the 61 patients entered in this study between November 3, 1983, and January 1986, four patients (three with neuroblastoma and one with Hodgkin's disease) were not evaluable for response because of early death from progressive tumor. Clinical evidence of response is shown in tables 2 and 3.

Three complete, 14 partial, and two mixed responses followed treatment of these 61 patients. Responses were seen in one-third of the patients with osteosarcoma. Twelve of these responses lasted ≥ 2 months. One complete response in a patient with brain metastases of osteosarcoma (table 3, Patient 1) has persisted for > 24 months. Patient 14 (table 3) developed recurrent pulmonary metastases of malignant Schwannoma 12 months after complete response had been achieved. Lesser proportions of patients with other major types of pediatric malignant solid tumors also had responses.

For patients who developed responses, the number of previous drug trials ranged from none to six (median, two trials) and the number of previous agents delivered ranged from none to eight (median, five agents). For patients failing to respond, the number of previous drug trials ranged from none to nine (median, three trials) and the number of previous agents delivered ranged from none to 12 (median, five agents).

One hundred forty-three treatment courses of ifosfamide were delivered; 61 patients received one course, 36 received two, nine received three, six received four, one received five, one received eight, and one received 11.

TABLE 2.—Patient diagnosis and responses following ifosfamide and mesna

Diagnosis	No. of patients	Response*				
		CR	PR	MR	SD	PD
Sarcoma						
Osteosarcoma	15	1	3	1	5	5
Rhabdomyosarcoma	5	—	2	—	—	3
Ewing's	2	—	—	—	—	2
Sarcoma, NOS†	2	—	1	—	—	1
Synovial cell	1	—	1	—	—	—
Leiomyosarcoma	1	—	—	—	1	—
Chondrosarcoma	1	—	—	—	—	1
Fibrosarcoma	1	—	—	1	—	—
Malignant fibrous histiocytoma	1	—	—	—	—	1
Malignant Schwannoma	1	1	—	—	—	—
Blastemal tumors						
Neuroblastoma	10	—	2	—	—	8
Wilms' tumor	6	—	2	—	—	4
Primitive neuroectodermal	1	—	1	—	—	—
Retinoblastoma	1	—	1	—	—	—
Hepatoblastoma	1	—	—	—	—	1
Carcinoma						
Nasopharyngeal	2	—	—	—	—	2
Hepatocellular	1	—	—	—	—	1
Dysgerminoma	1	—	1	—	—	—
Endodermal sinus	1	—	—	—	—	1
Lymphoma						
Hodgkin's	2	—	—	—	—	2
B-cell	1	1	—	—	—	—
Neuroectodermal						
Glioblastoma multiforme	2	—	—	—	1	1
Ependymoma	1	—	—	—	—	1
Melanoma	1	—	—	—	—	1
	61	3	14	2	7	35

*CR = complete response; PR = partial response; MR = mixed response; SD = stable disease; and PD = progressive disease.

†NOS = not otherwise specified.

Six courses were abbreviated because of severe nausea (one patient), seizures (two), or other neurotoxicity (three).

Nausea and vomiting was generally mild to moderate. A single antiemetic regimen was not used consistently for the patients in this study, although most patients received hydroxyzine pamoate (Vistaril).

Myelosuppression followed most treatment courses. The median wbc count nadir was $1600/mm^3$ (range, 300–7600) on Day 11 of Course 1 and was $1900/mm^3$ (range, 400–4600) on Day 14 of Course 2. Thirty-four of 61 patients had wbc counts $< 2000/mm^3$ during the first course and 17 of 36 evaluable patients had wbc counts $< 2000/mm^3$ during the second course. Significant thrombocytopenia was uncommon. Four patients developed platelet counts $< 50{,}000/mm^3$ during their first course of treatment, with a median nadir on Day 10; one patient developed a platelet count $< 50{,}000/mm^3$ following his second course of ifosfamide and mesna. In 12 patients who received more than four and up to 11 courses of ifosfamide and mesna, there was no evidence of cumulative myelosuppression.

Ten patients required hospital admission because of fever with associated neutropenia; infections included *Pseudomonas* septicemia in one patient, cellulitis in two, and infection of Hickman line site in two. The infections responded to appropriate antimicrobial therapy. The patient with *Pseudomonas* septicemia died because of bleeding from tumor (neuroblastoma) infiltration of the stomach and right kidney.

One patient developed urticaria following the 2nd day of ifosfamide and mesna in his second course of treatment. This directly followed the administration of mesna; iv administration of diphenylhydramine (Benadryl) prevented the recurrence of this effect.

Neurologic toxicity encountered in our patients has been previously reported (11). Briefly, it occurred in 13 patients who received 35 treatment courses of ifosfamide and mesna; these patients had 29 episodes of neurotoxicity. The usual symptoms of neurotoxicity were somnolence and weakness followed by confusion, tremors, hallucinations, ataxia, aphasia, urinary incontinence, and cranial nerve paralyses. Two patients developed seizures. Symptoms of neurotoxicity disappeared spontaneously within 72 hours of completion of the 5-day course of ifosfamide and mesna. Not all patients had recurrence of neurotoxicity with rechallenge with ifosfamide. Electroencephalograms were not of value in detecting neurotoxicity following ifosfamide and mesna in that generalized slowing and development of rhythmic delta wave activity were encountered in patients with and without evidence of neurotoxicity.

Hemorrhagic cystitis did not occur in any of the 61 patients. One patient developed hematuria after the third dose of ifosfamide in his first course; evaluation with cultures and voiding cystourethrogram failed to determine the etiology. This patient subsequently received ten full courses of ifosfamide and mesna because of persisting complete response of metastatic pulmonary nodules of malignant Schwannoma, without recurrence of hematuria. Two other patients had hematuria. One patient had known renal infiltration by neuroblastoma. Another patient, with primary osteosarcoma of the ilium, developed an atonic bladder secondary to primary tumor involving the prostate and presacral area; he developed hematuria only after requiring an indwelling catheter. After clearing of the hematuria he received two additional 5-day courses of ifosfamide and mesna without incident.

Renal toxicity as measured by increases of BUN and serum creatinine to greater than normal values was noted after seven of 143 treatment courses; each of these seven involved courses in patients who had received prior cisplatin (270–630 mg/m^2; median, 450 mg/m^2). In all patients, these changes were reversible. Two patients, who previously had received 400 and 540 mg/m^2 of cisplatin, had asymptomatic decrease of their serum magnesium level below normal ranges after receiving ifosfamide. There was no significant predisposition to clinically detected renal toxicity in patients who had previously received cisplatin. Subclinical nephrotoxicity associated with ifosfamide treatments was manifested

TABLE 3.—Responses following ifosfamide and mesna

Patient No.	Diagnosis	Response*	Duration of response (days)	No. of prior trials	No. of prior agents	Prior alkylating agents†
1	Osteosarcoma	CR	751+	1	2	DDP
2	Osteosarcoma	PR	80	3	5	DDP
3	Osteosarcoma	PR	52	1	6	Cy, DDP
4	Osteosarcoma	PR	94	1	3	Cy
5	Osteosarcoma	MR	71	2	7	Cy, DDP
6	Neuroblastoma	PR	42	5	6	Cy, DDP, L-PAM
7	Neuroblastoma	PR	89	2	4	Cy, DDP
8	Wilms' tumor	PR	45	2	5	DDP
9	Wilms' tumor	PR	49	3	5	DDP
10	Rhabdomyosarcoma	PR	111	4	6	Cy, L-PAM, DTIC
11	Rhabdomyosarcoma	PR	83+	2	5	Cy, DTIC
12	Synovial cell sarcoma	PR	56	2	5	Cy
13	Sarcoma, NOS‡	PR	146	3	6	Cy
14	Malignant Schwannoma	CR	362	0	0	None
15	Fibrosarcoma	MR	103	2	5	Cy
16	Retinoblastoma	PR	46	3	4	Cy
17	Dysgerminoma	PR	39	6	8	Cy, DDP
18	Primitive neuroectodermal tumor	PR	72	2	4	Cy, DDP
19	B-cell lymphoma	CR	45	3	8	Cy

* *See* table 2 for definitions.

†DDP = cisplatin; Cy = cyclophosphamide; L-PAM = melphalan, and DTIC = dacarbazine.

‡NOS = not otherwise specified.

by an increase in the excretion of the urinary enzymes *N*-acetylglucosaminidase and alanine aminopeptidase; elevations of posttreatment values above baseline pretreatment values were not so significant as elevations seen with cisplatin treatment.

Transient elevations of serum transaminase levels were observed with ten treatment courses delivered to eight patients. These exceeded twice normal levels following three treatment courses.

Capital alopecia developed in each of the patients who did not have alopecia at the start of ifosfamide treatment.

DISCUSSION

This study confirms the activity of ifosfamide in pediatric patients with recurrent tumors resistant to conventional modalities of treatment (5-8, 12-14). Patients with osteosarcoma, neuroblastoma, Wilms' tumor, rhabdomyosarcoma and other soft tissue sarcomas, primitive neuroectodermal tumor, retinoblastoma, and lymphoma responded. Although neither of our patients with Ewing's sarcoma responded, ifosfamide has been shown to have significant activity against this tumor (12). Additional patients, especially those with osteosarcoma, achieved stabilization of disease while receiving ifosfamide. The response rate of patients with metastatic osteosarcoma following ifosfamide, approximately 33%, is equal to the proportion responding after single-agent treatment with high-dose methotrexate, doxorubicin, or cisplatin (15). A recent report indicated that 11 of 21 patients with metastatic Wilms' tumor developed complete or positive responses following treatment with ifosfamide (16).

One of the more unusual and troublesome toxic effects of ifosfamide has been neurotoxicity, as described in several reports (1,5,6,8,17-19), including our own (11). Acidosis has been reported in association with the neurologic complications of ifosfamide therapy of adults with sarcomas (6), but was not detected in any of our patients.

Early clinical trials determined that a dose schedule of 6000 mg/m^2 in five divided daily doses was well-tolerated (20). At the time of initiation of this pediatric phase II study, the only information on dosage schedules for adults and children indicated the doses of ifosfamide tested ranged from 1.2 to 2.4 g/m^2 iv daily for 5 days (13). Classical phase I trials had not been performed on either adults or children. The dose of 1.6 g/m^2 iv daily was thus chosen as a moderate dose which probably would produce significant antitumor activity without life-threatening toxicity.

Also in early trials, hemorrhagic cystitis was the most troublesome toxic effect following ifosfamide (13). With the incidence of cystitis ranging up to 40% after treatment with ifosfamide, attempts were made at prevention and reduction of this toxic effect through the use of various uroprotectants including forced diuresis, sodium bicarbonate, ascorbic acid, *N*-acetylcysteine, and mesna (20). This toxic effect was reduced when ifosfamide was delivered in fractionated dosages with uroprotectants (2).

Brock et al (22) developed a large number of sulfhydryl-containing compounds which were effective in preventing hemorrhagic cystitis without reducing the antitumor effects of the alkylating agents. The most effective of these thiol compounds was sodium-2-mercaptoethane sulfonate, mesna (13,21,22), which counteracts the toxicity of acrolein on the bladder mucosa by form-ing adducts with thiols (23-26). Clinical studies involving 1270 patients receiving mesna with cyclophosphamide or ifosfamide indicated that 115 of the 1270 patients (9.5%) developed either gross or microscopic hematuria in comparison to 49 of 94 control patients (52%) treated without mesna (21). These studies led to the recommendations that ifosfamide not be delivered without simultaneous mesna. Our studies support the concept that mesna prevented the bladder toxicity but did not prevent a small proportion of patients from developing renal toxicity including azotemia, elevations of serum creatinine, and enzymuria, as reported previously (27,28).

Ifosfamide has shown a wide spectrum of antitumor activity in pediatric malignancies, some of which have previously been considered resistant to cyclophosphamide. Although ifosfamide and cyclophosphamide have similar antitumor spectra, ifosfamide appears to be the only alkylating agent to show significant response in osteosarcoma (7,15). Ifosfamide should be thoroughly evaluated for efficacy in such tumors. In solid tumors which have been shown to be sensitive to ifosfamide (ie, osteosarcoma and soft tissue sarcomas), studies to compare the relative efficacy of ifosfamide and cyclophosphamide in previously untreated patients are indicated. For certain tumors, such as osteosarcoma, consideration should be given to the inclusion of ifosfamide into phase II multiagent adjuvant trials.

REFERENCES

1. COHEN MH, CREAVEN PJ, TEJADA F, ET AL. Phase I clinical trial of iphosphamide (NSC-109724). Cancer Chemother Rep 59:751-755, 1975.
2. RODRIQUEZ V, BODEY GP, FREIREICH EJ, ET AL. Reduction of ifosfamide toxicity using dose fractionation. Cancer Res 36:2945-2948, 1976.
3. BURKETT H. Ifosfamide: European perspective. Semin Oncol 9: 28-35, 1982.
4. STUART-HARRIS RC, HARPER PG, PARSONS CA, ET AL. High dose alkylation therapy using ifosfamide infusion with MESNA in the treatment of adult advanced soft-tissue sarcoma. Cancer Chemother Pharmacol 11:69-72, 1983.
5. DE KRAKER J, and VOUTE PA. Ifosfamide, mesna and vincristine in pediatric oncology. Cancer Treat Rev 10(suppl A):165-166, 1983.
6. ANTMAN KH, MONTELLA D, ROSENBAUM C, ET AL. Phase II trial of ifosfamide with MESNA in previously treated metastatic sarcoma. Cancer Treat Rep 69:499-504, 1985.
7. MARTI C, KRONER T, REMAGEN W, ET AL. High-dose ifosfamide in advanced osteosarcoma. Cancer Treat Rep 69:115-117, 1985.
8. PINKERTON CR, ROGERS H, JAMES C, ET AL. A phase II study of ifosfamide in children with recurrent solid tumors. Cancer Chemother Pharmacol 15:258-262, 1985.
9. JURGENS H, BODE U, MULLER-WERHRICH S, ET AL. Phase II study of cisplatinum and ifosfamide in patients with recurrent Ewing's sarcoma. *In* Proceeding of the IVth NCI/EORTC Conference on New Drugs in Cancer Therapy, Abstract 117, 1983.
10. WHEELER BM, LOEHRER PJ, WILLIAMS SD, ET AL. Ifosfamide in refractory male germ cell tumors. J Clin Oncol 4:28-34, 1986.
11. PRATT CB, GREEN AA, HOROWITZ M, ET AL. Central nervous system toxicity following treatment of pediatric subjects with ifosfamide/MESNA. J Clin Oncol 4:1253-1261, 1986.
12. MAGRATH IT, SANDLUND JT, RAYNER A, ET AL. Treatment of recurrent sarcomas with ifosfamide (IF). Proc ASCO 4:136, 1985.
13. BRADE WP, HERDRICH K, and VARINI M. Ifosfamide—pharmacology, safety and therapeutic potential. Cancer Treat Rev 12:1-47, 1985.
14. ESCHENBACH C, MAROSKE D, and WINKLER K. Successful treatment of several metachromous pulmonary metastases of a chondroblastic osteosarcoma. Z Kinderchir 40:247-248, 1985.
15. PRATT CB. The treatment of metastatic ostersarcoma. *In* Pharmanual: Methotrexate in Osteogenic Sarcoma (Rosen G, ed). Chicago, PharmaLibri, 1984, pp 31-46.
16. TOURNADE MF, LEMERLE J, BRUNET-MONTIGNY M, ET AL. A phase II study of ifosfamide (Holoxan) in treatment of relapses in Wilms' tumor. *In* Proceedings of the XVIIth Meeting of the International Society for Paediatric Oncology, pp 208-209, Sept 30-Oct 4, 1985.
17. HEIM ME, FIENE R, SCHICK E, ET AL. Central nervous side effects following ifosfamide monotherapy of advanced renal carcinoma. J Cancer Res Clin Oncol 100:113-116, 1981.
18. MEANWELL CA, BLAKE AE, LATIEF TN, ET AL. Letter: Encephalopathy associated with ifosfamide/MESNA therapy. Lancet i:406-407, 1985.
19. CANTWELL BMJ, and HARRIS AL. Letter: Ifosfamide/MESNA and encephalopathy. Lancet i:752, 1985.
20. HANDELSMAN H, GOLDSMITH MA, and SLAVIK M. Clinical Brochure. Ifosfamide (NSC-109724). Bethesda, MD, National Cancer Institute, Mar 1974.
21. LUCE JK. MESNA. Background and Clinical Summary. Adria Laboratories, Columbus, OH, Oct 4, 1983.
22. BROCK N, POHL J, and STEKAR J. Studies on the urotoxicity of oxazaphosphorine cytostatics and its prevention. 2. Comparative study on the uroprotective efficacy of thiols and other sulfur compounds. Eur J Cancer Clin Oncol 17:1155-1163, 1981.
23. BROCK N, STEKAR J, and POHL J. Acrolein, the causative factor of urotoxic side-effects of cyclophosphamide, iphosphamide, trophosphamide and suphophosphamide. Arzneimittelforschung 29:659-668, 1979.
24. COX PJ. Cyclophosphamide cystitis—identification of acrolein as the causative agent. Biochem Pharmacol 28:2045-2049, 1979.
25. SCHEEF W, KLEIN HO, BROCK N, ET AL. Controlled clinical studies with an antidote against the urotoxicity of oxazaphosphorines: preliminary results. Cancer Treat Rep 63:501-505, 1979.
26. BRYANT BM, FORD HT, JARMAN M, ET AL. Prevention of isophosphamide induced urothelial toxicity with 2-mercaptoethane sulfonate sodium (Mesnum) in patients with advanced carcinoma. Lancet ii:657-659, 1980.
27. VAN DYK JJ, FALKSON HC, MERWE AM, ET AL. Unexpected toxicity in patients treated with iphosphamide. Cancer Res 32:921-924, 1972.
28. GOREN M, WRIGHT R, HOROWITZ M, ET AL. Urine enzymes, a sensitive indication of chemotherapy induced nephrotoxicity. Proc ASCO 4:43, 1985.

Prolonged Unmaintained Remission After Intensive Consolidation Therapy in Adult Acute Nonlymphocytic Leukemia[1,2]

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Thirty-five adults with acute nonlymphocytic leukemia who were in complete remission after initial induction therapy received a single course of high-dose cytarabine and amsacrine as consolidation therapy. No further therapy was administered. Despite substantial toxicity, the median duration of disease-free survival was 12 months, and 30% of patients are projected to be alive in continuous complete remission at 3 years. A single course of intensive postremission chemotherapy provides long-term disease-free survival in the absence of any further treatment. [Cancer Treat Rep 71:137-140, 1987]

Induction therapy of adult acute nonlymphocytic leukemia (ANLL) yields complete remission rates ranging from 65% to 80% (1). Long-term survival and cure of the disease by means of conventional chemotherapy requires that the patient remain in the initial complete remission. A variety of approaches have been employed to prolong remission duration including long-term maintenance therapy (2-6), additional intensive chemotherapy (consolidation) with (2,7,8) or without (7-9) subsequent maintenance therapy, or no further therapy (10). The median duration of remission in these studies ranges from 8 to 18 months, and it remains uncertain which of these postremission therapies produces superior long-term disease-free survival. Our randomized Eastern Cooperative Oncology Group (ECOG) study (2) of consolidation therapy suggested that the addition of two courses of attenuated induction therapy to maintenance therapy was better than maintenance therapy alone. This led us to question whether an intensive regimen, different from induction therapy, would enhance the potential benefit of consolidation therapy. ECOG's pilot study of high-dose cytarabine and amsacrine (HDARAC/AMSA) in relapsed ANLL produced a 70% complete remission rate (11). Because of its effectiveness, HDARAC/AMSA was selected for the current pilot study (PB482). Only a single course of treatment was administered; no maintenance therapy was employed because of its uncertain value. The aims of this study were to evaluate whether a single course of intensive postremission therapy could yield long, unmaintained remissions and whether the toxicity would be tolerable.

MATERIALS AND METHODS

Six ECOG member institutions participated in this trial. Adult patients, < 70 years old, with de novo ANLL were eligible for the study providing they satisfied the following eligibility criteria: morphologic proof of ANLL, FAB types M1 through M6 (12), as determined by repository center review of morphology and histochemistry by Dr. John Bennett; no previous treatment with chemotherapy or radiation therapy; $> 30\%$ marrow blasts; no prior hematologic disorders; no significant cardiac disease; adequate hepatic and renal functions; and documentation of informed consent.

Induction therapy consisted of one or two courses of

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daunorubicin (60 mg/m^2/day by iv push on Days 1-3); cytarabine (25 mg/m^2 by iv push followed by continuous iv infusion of 200 mg/m^2/day on Days 1-5); and 6-thioguanine (100 mg/m^2 orally every 12 hours on Days 1-5) (DAT). Patients with acute promyelocytic leukemia (FAB type M3) received heparin therapy during early induction treatment.

A single course of HDARAC/AMSA was given to patients achieving complete remission after resolution of complications of induction therapy. HDARAC/AMSA consisted of cytarabine at a dose of 3 g/m^2 every 12 hours by a 1-hour infusion for 12 doses on Days 1-6, followed by amsacrine at a dose of 100 mg/m^2/day by 1-hour infusion on Days 7-9. Patients were eligible for HDARAC/AMSA if they had a performance status of 2 or better (ECOG scale), no persisting infection, and adequate renal and hepatic functions. Prophylactic antibiotics were not employed. After completing this course of treatment, no further therapy was administered.

A total of 91 patients were registered for induction therapy between March 1982 and April 1984. Ten of these patients were ineligible for this study for the following reasons: three were diagnosed as having acute lymphocytic leukemia and one as having myelodysplasia ($< 30\%$ marrow blasts) after repository center review; four had pre-existing medical contraindications to entry in the study; and two were cancelled (died before therapy was administered). One patient was unevaluable because of a major protocol violation.

Complete remission was defined as an M1 marrow status ($< 5\%$ blasts, $> 15\%$ erythroid elements, $> 25\%$ normal myeloid elements, in a nonhypocellular marrow) and normal H1 peripheral blood (hemoglobin > 11 g/dl, neutrophil count $> 1500/\text{mm}^3$, no blasts, platelet count $> 100{,}000/\text{mm}^3$). Relapse was defined as the appearance of circulating leukemic cells or $> 5\%$ blasts in the bone marrow. Bone marrow aspiration to detect relapse was routinely performed every 2 months during the first 2 years of follow-up.

Remission duration distributions were computed using the Kaplan-Meier technique.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Entered	91
Ineligible/unevaluable	11
Eligible/evaluable	80
Median age in yrs (range): 46 (18-69)	
Complete remission rate*	56/80 (70)
Patients ≥ 60 yrs old	12/22 (55)
Patients < 60 yrs old	44/58 (76)
After 1 induction course	34/56 (61)
After 2 induction courses	22/56 (39)
Complete remission	
Consolidation	35
No consolidation	21
Patient refused	5
Medical complications of induction treatment	9
Relapse < 1 mo after remission	2
Allogeneic bone marrow transplantation	5

*Values = No. of patients with remission/total No. (%).

RESULTS

Induction Therapy

The median age of the 80 eligible patients (table 1) was 46 years (range, 18-69), and 28% of patients were ≥ 60 years old. The distribution of FAB types was: M1, 25%; M2, 19%; M3, 11%; M4, 25%; M5, 17%; and M6, 3%. The complete remission rate was 70% (56 remissions among 80 patients); 61% of the complete remissions occurred after a single course of induction therapy. A higher percentage of complete remissions occurred in patients < 60 years old than in older patients. These results are consistent with our previously reported study of this induction regimen (2).

Consolidation Therapy

Of the 56 patients achieving complete remission, 35 received the intended consolidation therapy with HDARAC/AMSA. Of the remaining 21 patients, five were referred for allogeneic bone marrow transplantation and 16 did not receive consolidation therapy for the reasons indicated in table 1. The median time from complete remission to the start of consolidation therapy was 29 days (range, 8-100). All patients received full doses of consolidation therapy.

A Kaplan-Meier plot of the probability of disease-free survival from the time of complete remission for patients receiving consolidation therapy appears in figure 1. For these patients, the median duration of remission is 12 months; 11 of 35 patients are in continuous complete remission at 18+ to 44+ months (median follow-up, 22 months), with an actuarial probability of remission at 24 and 36 months of 30% (95% confidence interval, ± 16%). The median survival of the patients receiving consolidation is 22 months, with an actuarial survival at 3 years of 38%.

The median duration of complete remission is 5 months for the nonconsolidated group; only two of 16 patients remain alive in initial remission at 21+ and 39+ months. Five patients, aged 18-29 years, did not receive consolidation and were referred for allogeneic bone marrow transplantation. Two of these patients died of infectious complications 1 and 2 months after transplant, one relapsed at 19 months, and two are alive in continuous complete remission at 22+ and 35+ months. In comparison, eight of the patients receiving consolidation were < 30 years old. Two of these patients died of infectious complications of consolidation, three relapsed at 9, 9, and 11 months, and three remain in continuous complete remission at 20+, 21+, and 28+ months.

Toxicity (table 2) of HDARAC/AMSA consolidation

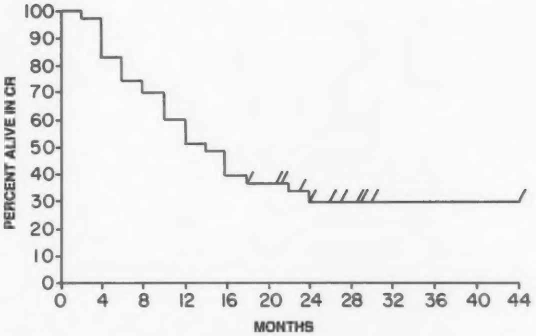

FIGURE 1.—Kaplan-Meier plot of probability of disease-free survival from the time of complete remission for 35 patients receiving HDARAC/AMSA consolidation. In this plot, any death is an event, even if patient was in remission at the time of death. Slash marks indicate individual patients alive and in complete remission at that time point. CR = complete remission.

therapy was substantial. As expected, the peripheral blood cell count nadir was prolonged, requiring a median 4 1/2 weeks for platelet and granulocyte counts to reach safe levels and 7 weeks to reach normal blood cell counts. High-dose cytarabine toxicity included diarrhea, which occurred in one-half of the patients, starting after the end of therapy and lasting for 7-10 days. Despite the routine administration of corticosteroid eye drops during therapy, 1/3 of the patients developed keratoconjunctivitis lasting for 3-4 days. Cytarabine-induced erythema occurred in 25% of patients; mucositis and liver dysfunction were infrequent and not severe. Cerebellar dysfunction was uncommon; it appeared in only two patients (46 and 63 years old) and was reversible.

The combination of gastrointestinal toxicity and prolonged myelosuppression was responsible for the high frequency of fungal infections (46%) and deaths (17%). Five of the six deaths from consolidation therapy were caused by fungal infections (table 2). All six patients who died were in complete remission at the time of their deaths, and two of these patients died of progressive fungal infection despite recovery of normal blood cell counts.

TABLE 2.—Consolidation toxicity

Toxicity	No. of patients (%)
Hematologic	
Median No. of days (range) from start of treatment to—	
> 500 granulocytes/mm^3: 33 (13-63)	
> 20,000 platelets/mm^3: 33 (15-74)	
Normal blood cell counts: 48 (30-112)	
Incidence in 35 patients	
Diarrhea	17 (50)
Rash	8 (23)
Keratoconjunctivitis	12 (34)
Mucositis	4 (11)
Liver dysfunction	3 (9)
Fungal infection	16 (46)
Cerebellar dysfunction	2 (6)
Deaths	6 (17)
Klebsiella sepsis	1
Candida sepsis	2
Phycomycosis	1
Aspergillus pneumonia	2

DISCUSSION

This pilot study shows that highly intensive postremission therapy with a single course of HDARAC/AMSA yields prolonged unmaintained remissions without any additional therapy. The median duration of complete remission was 12 months and 30% of patients are projected to be in continuous complete remission at 3 years. Although the 17% death rate in the current study raises the question of the safety of high-dose consolidation, awareness of potential complications and early appropriate therapy of presumptive fungal infections can substantially reduce the risks. In an ongoing ECOG study which randomizes patients to postremission therapy with HDARAC/AMSA, there have been no deaths among the initial 28 patients treated with the HDARAC/AMSA regimen. Improved survivorship during consolidation therapy is likely to increase the long-term survival from this treatment.

Most patients in complete remission after induction therapy have occult residual leukemic cells in the marrow and other tissues. Regrowth of these cells leads to relapse in the great majority of patients. Postremission therapy is therefore directed at reducing the number of remaining leukemic cells to delay relapse or effect a cure. Long-term low-dose maintenance therapy yields median remission durations of 8-18 months, with 13%-25% of patients remaining in complete remission at 3 years (2-5). In a randomized ECOG study, the addition of one or two courses of attenuated doses of induction therapy prior to the institution of maintenance therapy improved the 3-year disease-free survival, without altering the median duration of remission (2). Recent studies have escalated the intensity of consolidation by employing full doses of induction therapy. In one study, patients in complete remission received one to three cycles of induction therapy before randomization to maintenance or no further therapy (7). The median duration of remission of 18 months and the 3-year disease-free survival rate of 23% did not differ between the two groups. However, patients had to remain in remission for several months to reach the randomization step, and 21% relapsed before randomization. The authors' conclusion that maintenance treatment after consolidation therapy offered no additional benefit applies only to patients who do not experience early relapse. Another study reached the opposite conclusion (8). Patients received a single course of the induction therapy regimen as consolidation before randomization to maintenance therapy or no further treatment. Follow-up maintenance therapy provided a 13-month median duration of remission, with 30% projected to be in remission at 2 1/2 years versus 8 months and 17% in the no further therapy group. These two studies (7,8) are not directly comparable because they utilized a different number of consolidation courses. The value of maintenance therapy after intensive consolidation thus remains in doubt.

Further escalation of the intensity of consolidation therapy in nonrandomized trials employing no maintenance therapy strongly suggests that aggressive consolidation therapy produces remission durations that are as long or longer than the results of current maintenance therapy regimens (9,10,13,14). Champlin et al (9) treated patients in remission with one course of 5-azacitidine plus doxorubicin followed (in one-half of the patients) by one course of the induction therapy regimen. The median duration of remission was 14 months, and 26% of patients are in complete remission at 3 years. Vaughan et al (10) repeated their high-dose cytarabine/daunorubicin induction regimen as a single consolidation course. Their actuarial projection was a 3-year disease-free survival rate of 44%. In an approach similar to the current study, one or two courses of high-dose cytarabine with or without daunorubicin were used as consolidation therapy by Wolff et al (13), resulting in a projected 50% 3-year disease-free survival rate. It may be that consolidation therapy, as in the current study, with regimens which are different from and/or more intensive than conventional induction therapy can enhance the percentage of long-term disease-free survivors. The 3-year disease-free survival rates of these recent studies are similar to the outcome after allogeneic bone marrow transplantation in adults with ANLL (14). If these results are confirmed in ongoing nonselected randomized trials, then chemotherapy for ANLL in first remission may prove to be at least as effective and more broadly applicable than allogeneic bone marrow transplantation (15–18).

REFERENCES

1. BLOOMFIELD CD. Postremission therapy in acute myeloid leukemia. J Clin Oncol 13:1570–1572, 1985.
2. CASSILETH PA, BEGG CB, BENNETT JM, ET AL. A randomized study of the efficacy of consolidation therapy in adult acute nonlymphocytic leukemia. Blood 63:843–847, 1984.
3. YATES J, GLIDEWELL O, WIERNIK P, ET AL. Cytosine arabinoside with daunorubicin or adriamycin for therapy of acute myelocytic leukemia: a CALGB study. Blood 60:454–461, 1982.
4. PETERSON BA, and BLOOMFIELD CD. Prolonged maintained remissions of adult acute non-lymphocytic leukemia. Lancet 2:158–160, 1977.
5. RAI KR, HOLLAND JF, GLIDEWELL OJ, ET AL. Treatment of acute myelocytic leukemia: a study by Cancer and Leukemia Group B. Blood 58:1203–1212, 1981.
6. GLUCKSBERG H, CHEEVER MA, FAREWELL VT, ET AL. High-dose combination chemotherapy for acute nonlymphoblastic leukemia in adults. Cancer 48:1073–1081, 1981.
7. SAUTER C, FOPP M, IMBACH P, ET AL. Acute myelogenous leukaemia: maintenance chemotherapy after early consolidation treatment does not prolong survival. Lancet 1:379–382, 1984.
8. BUCHNER R, URBANTIZ D, HIDDEMANN W, ET AL. Intensified induction and consolidation with or without maintenance chemotherapy for acute myeloid leukemia (AML): two multicenter studies of the German AML Cooperative Group. J Clin Oncol 3:1583–1589, 1985.
9. CHAMPLIN R, GALE RP, ELASHOFF R, ET AL. Prolonged survival in acute myelogenous leukemia without maintenance therapy. Lancet 1:894–896, 1984.
10. VAUGHAN WP, KARP JE, and BURKE PJ. Two-cycle timed-sequential chemotherapy for adult acute nonlymphocytic leukemia. Blood 64:975–980, 1984.
11. HINES JD, OKEN MM, MAZZA JJ, ET AL. High-dose cytosine arabinoside and *m*-AMSA is effective therapy in relapsed acute nonlymphocytic leukemia. J Clin Oncol 2:545–548, 1984.
12. BENNETT JM, CATOVKSY D, DANIEL MT, ET AL. Proposed revised criteria for the classification of acute myeloid leukemia. Ann Intern Med 103:626–629, 1985.
13. WOLFF SN, MARION J, STEIN RS, ET AL. High-dose cytosine arabinoside and daunorubicin as consolidation therapy for acute nonlymphocytic leukemia in first remission: a pilot study. Blood 65:1407–1411, 1985.
14. O'REILLY RJ. Allogeneic bone marrow transplantation: current status and future directions. Blood 62:941–964, 1983.
15. MAYER RJ, WEINSTEIN HJ, CORAL FS, ET AL. The role of intensive postinduction chemotherapy in the management of patients with acute myelogenous leukemia. Cancer Treat Rep 66:1455–1462, 1982.
16. PREISLER HD. Therapy for patients with acute myelocytic leukemia who enter remission: bone marrow transplantation or chemotherapy? Cancer Treat Rep 66:1467–1473, 1982.
17. CHAMPLIN RE, HO WG, GALE RP, ET AL. Treatment of acute myelogenous leukemia: a prospective controlled trial of bone marrow transplantation versus consolidation chemotherapy. Ann Intern Med 102:285–291, 1985.
18. APPELBAUM FR, DAHLBERG S, THOMAS ED, ET AL. Bone marrow transplantation or chemotherapy after remission induction for adults with acute nonlymphoblastic leukemia: a productive comparison. Ann Intern Med 101:581–588, 1984.

Phase I Trial of Tiazofurin Administered by Iv Bolus Daily for 5 Days, With Pharmacokinetic Evaluation[1,2]

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Tiazofurin is a novel C-nucleoside with significant antitumor activity in murine tumor models. In a phase I clinical trial, patients received tiazofurin by bolus iv infusion daily for 5 days. Six doses ranging from 550 to 4100 mg/m^2/day were evaluated. Thirty-one treatment courses were initiated in 21 patients. Tiazofurin induced multiple, transient toxic effects at all but the lowest dose level, and treatment interruption was a common result. Nine of 28 treatment courses initiated at doses $\geq$ 1100 mg/m^2/day were interrupted at $<$ 5 days; only five of eight courses initiated at 1100 mg/m^2/day were completed. Symptoms leading to treatment interruption included headache, nausea and emesis, and lethargy and malaise. Other significant, transient toxic effects included skeletal muscle injury manifest as pain, weakness, or serum biochemical abnormalities; mucocutaneous effects; and mental or mood changes. One case each of transient pericarditis and fatal cardiomyopathy occurred at the highest dose. Myelosuppression was observed but was transient and not dose limiting. In addition to leukopenia and thrombocytopenia, unexpected declines in serum hemoglobin were observed, although these were of uncertain significance. Tiazofurin induced significant increases in uric acid production which could be reversed with coadministration of allopurinol. Pharmacokinetic analysis revealed tiazofurin plasma elimination to be at least biphasic, with a β-half-time of 4.2 hours; most of an injected dose could be recovered from the urine as unaltered compound within 24 hours. From this study we conclude that an appropriate dose for phase II trials with this schedule is $\leq$ 1000 mg/m^2/day. The schedule may be a difficult one for clinical evaluation of antitumor activity, however, because of the possibility of frequent treatment interruption due to multiple systemic toxic effects. [Cancer Treat Rep 71:141-149, 1987]

Tiazofurin (2-β-D-ribofuranosylthiazole-4-carboxamide; NSC-286193), a novel thiazole C-nucleoside, is the prototype of a new class of oncolytic agents (fig 1) (1). Tiazofurin has potent oncolytic activity in several murine tumor systems including P388 leukemia, L1210 leukemia, and the commonly refractory Lewis lung carcinoma (1-3). Investigations of mechanism of action indicate that tiazofurin cytotoxicity is mediated by guanine nucleotide depletion (4). Tiazofurin is metabolized to tiazofurin adenine dinucleotide (TAD), an analog of nicotinamide adenine dinucleotide (NAD) (5). TAD is inhibitory for inosine monophosphate dehydrogenase (IMP:NAD oxireductase, EC 1.2.1.14; IMPD), an NAD-dependent enzyme of the de novo guanine nucleotide synthetic pathway. Reduced guanine nucleotide pools lead to reduced DNA and RNA synthesis with cytotoxic effects (4). The selenium-substituted tiazofurin analog selenazofurin has a similar mechanism of action and similar biochemical effects (6). Other IMPD inhibitors, mycophenolic acid, ribavirin, and aminothiadiazole,

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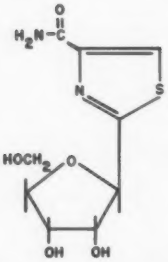

FIGURE 1.—Structure of tiazofurin.

have similar, but not identical, cellular biochemical effects (4,7–9). Cytotoxic effects of tiazofurin may reflect mechanisms of action other than inhibition of IMPD. Incubation of L1210 cells with tiazofurin induces diminished NAD synthesis and modest inhibition of poly-(ADP-ribose)polymerase (EC 2.4.2.30), an NAD-dependent enzyme which functions in DNA repair (10).

Preclinical toxicity studies in mice and dogs utilizing single dose and daily bolus × 5 schedules have been reported (11). In toxic doses tiazofurin induces a systemic state of lethargy, prostration, and hypothermia, as well as specific adverse effects upon the hematopoietic, gastrointestinal, hepatic, renal, and endocrine systems. With a daily bolus × 5 schedule, the murine 10% lethal dose was 5481 $mg/m^2/day$. At this dose, no toxic signs were observed in dogs.

This is a report of a phase I clinical trial of tiazofurin administered by iv bolus daily for 5 days, with pharmacokinetic evaluation. Similar studies in adults and children have been reported previously (12–16).

METHODS

Persons $\geq$ 18 years old with histopathologically diagnosed cancer for whom at the time of entry conventional or other investigational therapies offered no reasonable expectation of benefit were eligible for this trial. Eligibility requirements included adequate bone marrow, renal, and hepatic function (wbc count $> 4000/\mu l$, platelet count $> 100{,}000/\mu l$, creatinine ≤ 2.5 mg/dl, and bilirubin ≤ 2.5 mg/dl); estimated life expectancy of at least 12 weeks; and Karnofsky performance status > 30. Patients must not have had any chemotherapy or irradiation within 30 days of entry into the trial. The study protocol fulfilled federal and University of Vermont institutional requirements for human experimentation, and all entrants gave an informed consent. Although measurable or evaluable disease was not an eligibility requirement, an evaluation of disease response was made whenever possible.

Pretreatment evaluation included a complete history and physical examination; cbc; serum chemistry profile including uric acid, albumin, total protein, alkaline phosphatase, glutamic oxaloacetate transaminase, calcium, phosphorus, and electrolytes; urinalysis; and examination of a bone marrow aspirate and biopsy specimen. Most patients were treated in the University of Vermont Clinical Research Center inpatient unit; two treatment courses were initiated on an outpatient basis. During treatment each patient was interviewed and examined daily, and blood cell counts and serum uric acid levels were measured daily. After treatment, blood cell counts and urinalyses were done twice weekly and serum chemistries were done weekly for at least 3 weeks and until resolution of any apparent toxic effects. Patients were interviewed and examined for signs of toxicity 3 weeks after completion of therapy or more frequently as indicated. In the course of the trial skeletal muscle toxicity was observed, and, subsequently, frequent serum creatine phosphokinase (CPK) and CPK isoenzyme levels and resting electrocardiograms were obtained.

Tiazofurin for administration was obtained from the National Cancer Institute, formulated as a freeze-dried solid packaged in 10-ml vials containing 1 g of tiazofurin, 200 mg of mannitol, and sodium hydroxide/hydrochloric acid for pH adjustment. Upon reconstitution with 4.6 ml of sterile water for injection, this yielded a solution of estimated pH 6.0–7.5. Tiazofurin was further diluted in 100 ml of saline prior to administration.

Patients received tiazofurin by 10-minute iv infusion daily for 5 days. Individual doses were calculated on the basis of idealized body surface area derived from a nomogram based upon height and weight with input of the lower of actual or ideal body weight. The initial dose level, 550 $mg/m^2/day$, represented one-tenth the mouse 10% lethal dose. At least three patients were entered at each dose level. Individual patients not experiencing dose-limiting toxic effects were eligible for re-entry at a subsequent dose level. Dose was escalated from 550 to 4100 $mg/m^2/day$ in five steps, initially by doubling and subsequently by 25% increments.

Additional blood and urine specimens were obtained for pharmacokinetic analysis and evaluation of alterations in purine metabolism. Blood samples for pharmacokinetic analysis were drawn 0.25, 0.50, 1, 2, 4, 8, and 24 hours after initiation of drug infusion from selected patients on Days 1, 3, and/or 5 of treatment. Additional samples were collected in selected patients. Blood samples for purine analysis were drawn daily during treatment. Blood samples were left at room temperature for 1 hour, after which the serum was separated and frozen for later analysis. Complete daily urine collections were obtained for analysis of tiazofurin and purine excretion. Urine samples were collected in 6-hour intervals for refrigeration, and an aliquot was frozen at the conclusion of each treatment day for later analysis. Tiazofurin content was analyzed by a technique previously reported (17). In brief, serum samples were diluted with 5 volumes of acetonitrile and centrifuged. The supernatants were concentrated and aliquots were spotted on Avicel-F (250-μm particle size) plates and developed in propanol/water (70/30). Tiazofurin was visualized under a UV light; samples were scraped, resuspended in water, sonicated, and subjected to high-performance liquid chromatography (HPLC) utilizing a 10-μm C_{18} μBondapak column (Waters Associates, Milford, MA) with mobile-phase 0.02 M sodium acetate (pH 4.5)/methanol (98/2) at a flow rate of 2.5 ml/minute with UV detection at 235 nm. Two-phase polyexponential models were fit to the serum concentration data in order to estimate pharmacokinetic parameters (18). The time of drug infusion was subtracted from all sample times before fitting; that is, the data were analyzed as if the drug had been administered by instantaneous bolus infusion. Data input into a model accounting for the 10-minute constant infusion yielded essentially the same parameter estimates. Weighted (1/y) and unweighted fits were compared; the analysis is reported based upon the unweighted fits. When appropriate, averages were calculated as weighted averages weighted by the reciprocal standard error (ie, precision).

Xanthine, hypoxanthine, and uric acid content in serum and purine and tiazofurin content in urine were analyzed by HPLC utilizing a 5-μm C_{18} Chromasil column (American Scientific Products, Bedford, MA) with a 5-μm C_{18} guard column with mobile-phase 0.02 M KH_2PO_4 (pH 3.65) at a flow rate of 2.5 ml/minute with UV detection at 254 nm in a modification of previously reported techniques (19,20). Uric acid content as determined by HPLC was confirmed utilizing an enzymatic-colorimetric assay based upon previously reported techniques available as a commercially prepared kit from Sigma Chemical Co (21,22).

RESULTS

The characteristics of 21 patients enrolled in a phase I trial of tiazofurin administered by iv bolus daily for 5 days are summarized in table 1.

TABLE 1.—Tiazofurin: patient characteristics

	No. of patients
Entered	21
Gender	
Male	10
Female	11
Age (yrs)	
Median: 58	
Range: 23–71	
Performance status (Karnofsky)	
Median: 90	
Range: 50–100	
Serum creatinine (mg/dl)	
Median: 0.9	
Range: 0.6–1.6	
Prior treatment	
Radiation therapy	1
Chemotherapy	7
Chemotherapy and radiation therapy	9
None	4
Tumor diagnosis	
Non-small cell lung carcinoma	2
Breast carcinoma	1
Pancreatic carcinoma	3
Melanoma	1
Fibrosarcoma	1
Esophageal carcinoma	1
Colon carcinoma	6
Mixed mesodermal carcinoma of the uterus	1
Undifferentiated carcinoma, primary unknown	1
Adenocarcinoma, primary unknown	1
Neuroblastoma	1
Non-Hodgkin's lymphoma	1
Non-small cell lung carcinoma and non-Hodgkin's lymphoma	1

Toxicity

Patient intolerance of multiple, transient toxic effects was the treatment-limiting phenomenon in this trial. Five doses of drug were administered in only 22 of 31 courses initiated. In seven of the nine courses not completed, treatment was stopped at the patient's request. Failure to complete a 5-day course occurred at all dose levels except the lowest. Table 2 summarizes the experience of course completion by dose.

Symptoms contributing to patient intolerance involved multiple systems (table 3). Headache was common and occurred in 22 of 31 courses and at all doses except the lowest. Onset of headache typically occurred hours after infusion of the first dose and recurred with subsequent doses. Headache often was severe and responded incompletely to acetaminophen or oral narcotic medications. Nausea occurred in 12 of 31 courses and emesis in 9 of 31 courses; each occurred at all doses greater than the lowest. Nausea and emesis typically were accompanied by headache. They usually resolved after several hours but recurred with subsequent doses, and they frequently were refractory to one or several antiemetic medications given orally or parenterally. Lethargy and malaise were reported in 12 of 31 courses and at all doses greater than the lowest; in all but one case these symptoms were accompanied by headache. Pain, apparently of muscle origin, was experienced in six of 31 courses, most frequently at the highest dose. Myalgia typically involved the paraspinal and proximal extremity musculature. Onset of myalgia typically was delayed until the second, third, or fourth day of treatment. For two patients myalgia contributed to a decision to discontinue treatment.

Observation of myalgia prompted prospective evaluations of serum CPK levels. CPK elevations, which ranged from small to 20-fold increases, were observed throughout the dose range evaluated, including six of seven courses at the highest dose. Half the patients with CPK abnormalities were asymptomatic. CPK isoenzyme determinations uniformly indicated an abnormality of skeletal muscle only. Onset of CPK elevation ranged from Day 3 to Day 11, with a median duration of 1 week. One patient treated at 1100 mg/m^2/day presented on the scheduled fifth day of treatment with proximal extremity myalgia and weakness with inability to rise from a recumbent position; CPK at the time was normal.

TABLE 2.—Tiazofurin: course completion by dose

Dose*	Courses initiated	Patients entered†	Patients completing a course‡	Courses completed
550	3	3	3	3
1100	8	7	4	5
2200	5	4	3	3
2700	4	4	3	3
3300	3	3	3	3
4100	8	7	4	5
All	31			22

*mg/m^2/day × 5.

†Total No. of patients treated at a dose level.

‡Total No. of patients completing at least 1 treatment course at a dose level.

Treatment was discontinued, and the patient's condition reversed over 48 hours.

In four courses, three at the highest dose, patients complained of unpleasant mental or mood changes such as anxiety or mind-body dissociative sensations.

Hyperuricemia and hyperuricosuria were anticipated effects of tiazofurin-induced blockade of guanine nucleotide synthesis from IMP. A modest elevation in serum uric acid and an increase in urine uric acid excretion from 800 to 1600 mg/day occurred in the first patient treated (fig 2). Subsequently, allopurinol (300 mg/day) was administered either upon initiation of tiazofurin treatment or upon observation of an increasing serum uric acid expected to exceed 10 mg/dl. Once initiated, allopurinol was administered 1 day beyond tiazofurin treatment. In 13 completed courses at doses ranging from 550 to 4100 mg/m^2/day, treatment was initiated without allopurinol; in eight of these, allopurinol was instituted on Day 2 or Day 3 in order to reverse progressive hyperuricemia. The five courses in which allopurinol treatment was not required included one at each of the three highest dose levels. No differences in the frequency of course completion or other acute or delayed toxicity were apparent in this limited sample between patients receiving and patients not receiving allopurinol. In selected patients, purine (uric acid, hypoxanthine, and xanthine) content was analyzed in serum (nine courses) and urine (six of nine courses) on a daily basis. In three of these, allopurinol was not required; in four, allopurinol was instituted for progressive hyperuricemia; and in two, allopurinol was administered prophylactically. Tiazofurin-induced peaks for serum purine content and 24-hour urine purine excretion are shown in table 4. Patients not receiving allopurinol generally demonstrated increases in serum levels of all purines, but only uric acid levels approached or exceeded solubility limits. In these patients, urine excretion of uric acid and xanthine, but not hypoxanthine, exceeded solubility limits. In courses in which allopurinol was instituted to reverse progressive hyperuricemia, prompt reciprocal changes in uric acid and precursor purine levels occurred, with declines of uric acid in serum and urine and increases of hypoxanthine and xanthine. In courses in which allopurinol was administered prophylactically, no purines approached solubility limits in serum; however, urine excretion of both uric acid and xanthine exceeded solubility limits.

TABLE 3.—Tiazofurin: summary of toxicity*

Toxic effect	No. of occurrences/No. of evaluable courses at each drug dose (mg/m^2/day)					
	550	1100	2200	2700	3300	4100
Nausea	0/3	2/8	3/5	2/4	1/3	4/8
Emesis	0/3	2/8	1/5	2/4	1/3	3/8
Headache	0/3	5/8	5/5	3/4	2/3	7/8
Lethargy/malaise	0/3	3/8	3/5	3/4	0/3	3/8
Mental/mood changes	0/3	1/8	0/5	0/4	0/3	3/8
Myalgia	0/3	1/8	1/5	0/4	1/3	3/8
Weakness	0/3	1/8	0/5	0/4	0/3	0/8
CPK elevation	—	2/5	—	2/4	1/2	6/7
Pericarditis	0/3	0/8	0/5	0/4	0/3	1/8
Abnormal taste/dry mouth	0/3	1/8	2/5	1/4	0/3	1/8
Desquamation	0/3	0/8	2/5	2/4	1/3	3/6
Conjunctivitis	0/3	0/8	1/5	2/4	0/3	0/8
Erythematous rash	0/3	1/8	1/5	0/4	0/3	1/8

*Excludes hematologic toxicity, abnormalities of purine metabolism, and 1 death. Dash = not evaluated.

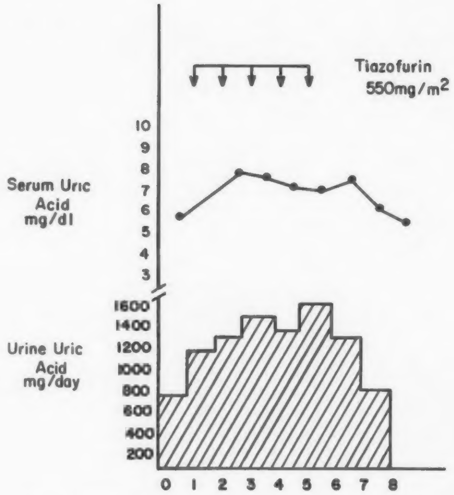

FIGURE 2.—Effect of tiazofurin (550 mg/m^2/day × 5) upon serum uric acid and urine uric acid excretion.

Variable, transient, non-dose-limiting leukopenia and thrombocytopenia were observed at all doses except the lowest (table 5). Leukocyte nadirs frequently occurred in the third or fourth week after initiation of treatment. Patients with significant prior exposure to cytotoxic agents appear to have experienced more profound cytopenias.

An unusual incidence of onset or exacerbation of

TABLE 4.—Tiazofurin: peak serum concentration and urine excretion of purines*

Patient/ course	Dose (mg/m^2)	Allopurinol†	Serum purine (mg/L)			Urine purine (mg/24 hrs)		
			Uric acid	Hypoxanthine	Xanthine	Uric acid	Hypoxanthine	Xanthine
7/1	2700	—	87	4.6	1.8	1097	54	4
7/2	3300	3	108	6.8	7.5			
8/1	2700	3	123	2.9	5.9	851	475	182
9/1	3300	3	121	7.0	8.2			
10/1	3300	—	98	0.9	1.5			
11/1	4100	—	60	1.6	1.4	1509	83	27
12/1	4100	2	98	10.8	9.5	625	792	202
12/2	4100	−1	20	11.4	10.6	353	1123	359
13/1	4100	−1	24	2.8	2.2	848	549	285
Solubility limits‡			70	1150	100	150	1400	50

*Peak values for daily serum samples and 24-hr urine collections during a 5-day course of treatment.

†Day of initiation of allopurinol. Once initiated, allopurinol was continued 1 day beyond last treatment day. Prophylactic treatment, initiated 1 day prior to tiazofurin, indicated by "−1".

‡Solubility limits (mg/L) for purine in serum or urine (pH 5) (*from* Klinenberg JR, Goldfinger SF, and Seegmiller JD: The effectiveness of a xanthine oxidase inhibitor allopurinol in the treatment of gout. Ann Intern Med 62:639, 1965).

anemia, frequently necessitating rbc transfusion, occurred in the course of this study. All ten patients completing a 5-day course at doses ≥ 2700 mg/m^2/day experienced a decline in hemoglobin concentration of at least 2 g/dl (table 6). The median nadir day was Day 13. Observation of the magnitude and kinetics of hemoglobin changes was incomplete in four patients due to the need to initiate transfusion therapy. In a population of chronically ill patients undergoing repeated phlebotomy for toxicity monitoring and pharmacokinetic studies, it is difficult to determine whether a decline in hemoglobin concentration reflects, in addition, a toxic effect upon erythrocyte production or survival. The incidence and severity of new or exacerbated anemia in this study was exceptional in comparison to observations in similar trials of other agents conducted at this institution. No biochemical evidence of acute hemolysis (elevated bilirubin) was observed, and fecal testing revealed no cases of occult gastrointestinal hemorrhage.

Several types of reversible mucocutaneous toxicity occurred in the course of this study (table 3). The most common was desquamation usually affecting the hands and feet and occurring in the second week. Conjunctivitis and an erythematous rash primarily of the hands and face each occurred on three occasions, and in all but one case these heralded subsequent desquamation. No cases of mucocutaneous toxicity led to interruption of treatment.

Dose-limiting toxic effects were observed in two of eight treatment courses initiated at 4100 mg/m^2/day. In one patient, acute pericarditis was diagnosed on the fourth treatment day on the basis of the onset of chest pain associated with a pericardial friction rub and ECG changes. At the same time, this patient experienced significant myalgia, especially of the paraspinal muscles. These symptoms were associated with a marked elevation of serum CPK limited to the skeletal isoenzyme fraction. Tiazofurin treatment was discontinued, and all toxic effects resolved over several days. This patient was treated subsequently at 1100 mg/m^2/day × 5 without a recurrence of symptoms but with minor skeletal muscle CPK elevations.

TABLE 5.—Tiazofurin: hematologic toxicity*

Dose (mg/m^2/day × 5)	Courses initiated/ courses evaluable	Wbc count nadir		Platelet count nadir	
		Median count (range)†	Median Day (range)	Median count (range)†	Median Day (range)
550	3/3	4.3 (3.9–5.7)	4 (4–15)	97 (95–106)	9 (4–18)
1100	8/5	5.7 (4.7–6.8)	21 (4–28)	277 (42–385)	13 (5–21)
2200	5/3	7.0 (1.5–9.0)	16 (0–23)	17 (6–150)	18 (16–22)
2700	4/3	5.7 (3.6–11.6)	25 (5–27)	116 (114–349)	12 (8–12)
3300	3/3	7.1 (1.9–7.7)	23 (23–25)	160 (121–223)	15 (14–17)
4100	8/4	3.2 (1.8–9.5)	23 (18–27)	172 (54–344)	15 (13–16)

*Excludes rbc toxicity. *See* text.

†$\times 10^{-3}/\mu l$.

TABLE 6.—Tiazofurin: hemoglobin changes at doses ≥ 2700 mg/m^2/day × 5

	No. of courses
Evaluable	10
Hemoglobin decline (g/dl)	
≥ 2	10
≥ 3	6
≥ 4	2
Transfusion given	4

One apparent tiazofurin-related death occurred in this study. The patient was a 62-year-old woman with adenocarcinoma of unknown primary with abdominal carcinomatosis who had received prior cytotoxic therapy including doxorubicin (260 mg/m^2). Her only other medical problem was a history of migraine for which she received prophylactic propranolol (40 mg daily). She received tiazofurin at a dose of 4100 mg/m^2/day for 5 days, during which time she experienced headache, nausea, and emesis treated symptomatically with antiemetics, analgesics, and sedatives. On the morning of the sixth day she awoke lethargic and suffered a fall. Neurologic exam revealed no focal deficit, and a computerized tomographic scan of the brain was normal. Serum CPK at this time was elevated eightfold due to abnormality of the skeletal muscle isoenzyme fraction. The evening of the sixth day the patient experienced the rapid onset of respiratory distress, cardiorespiratory arrest, and death despite resuscitative efforts. In addition to abdominal carcinomatosis, autopsy revealed abnormalities of the heart and brain. The myocardium was affected by a focal, acute, necrotizing and inflammatory process which did not follow a vascular distribution and was not associated with coronary atherosclerosis. These changes were consistent with an acute inflammatory cardiomyopathy. Within the brain, multiple hemorrhagic infarcts, 12-24 hours of age, were distributed diffusely in both hemispheres.

Pharmacokinetics (see table 7 and figure 3)

Day-1 peak tiazofurin serum levels in three patients receiving the highest dose (4100 mg/m^2) ranged from 197 to 308 μg/ml. Measurable drug persisted in the serum for 24 hours at all doses tested, with first-day trough levels ranging from 2 to 9 μg/ml. The apparent Day-1 β-phase elimination half-time ranged from 2.7 to 9.8 hours, with a weighted average of 4.2 hours (weighted by standard error). Although three-phase models were attempted, a longer phase could not be estimated from the available data. A contrast of the β-half-times of Day 1 versus Day 3 from 12 courses at doses ranging from 2200 to 4100 mg/m^2 did not reveal significant changes between these days. There was a statistically significant inverse relation between dose and β-half-time for the Day-1 data, but the difference was clinically negligible. The primary route of elimination was renal excretion.

TABLE 7.—Tiazofurin: pharmacokinetics and urine excretion on Day 1

Patient/ course	Serum creatinine (mg/dl)	Dose (mg/m^2)	Peak serum concentration (μg/ml)	24-hr serum concentration (μg/ml)*	$t_{1/2}\alpha$ (hr)	$t_{1/2}\beta$ (hr)	Clearance (L/hr × m^2)	Volume of distribution, area (L/m^2)	Area under curve (hr × μg/ml)	Urine excretion (fraction of dose administered)
1/1†	1.0	1100	50	2	0.91	9.73‡	4.51	63.6	244	
2/1§	1.3	1100	41	2	0.71	6.92	4.56	45.6	241	
3/1¶	1.0	1100	48	ND	0.52	5.17	5.02	37.4	219	
4/2**	0.9	2200	92	ND	0.14	3.51	6.53	33.2	337	
5/2¶	1.1	2200	121	8	0.94	8.69	3.25	40.7	676	
6/2††	0.8	2700	118	6	0.15	2.65	8.74	33.5	309	
7/1	0.6	2700	103	3	0.91	9.78‡	6.84	96.4	395	
8/1	0.6	2700	109	9	0.46	6.02	4.35	37.8	621	
7/2	0.6	3300	120	3	0.19	3.50	6.48	32.7	509	
9/1	0.8	3300	112	2	0.23	3.28	10.55	50.0	313	
10/1	0.8	3300	118	4	0.77‡	3.96‡	6.92	39.5	477	
11/1	1.2	4100	197	8	0.23	6.47	4.42	41.3	928	
12/1	0.8	4100	230	5	0.20	3.91	5.50	31.1	746	0.54
12/2§	0.8	4100	308	7	0.27	4.41	4.56	29.0	889	0.93
13/1§	0.6	4100	156	2	3.17‡	4.01‡	5.58	32.3	734	0.76
					0.26‡‡	4.18‡‡	5.85 ± 1.90§§	42.9 ± 17.2§§	510 ± 242§§	

*ND = not done.

†Additional data points: 12 hrs, 16 hrs.

‡Imprecise estimate: t-score < 2.

§Additional data points: 12 hrs, 16 hrs, 20 hrs.

¶Omitted data point: 24 hrs.

**Omitted data points: 8 hrs, 24 hrs.

††Additional data point: 20 hrs.

‡‡Weighted average, weighted by standard error.

§§Mean ± standard deviation.

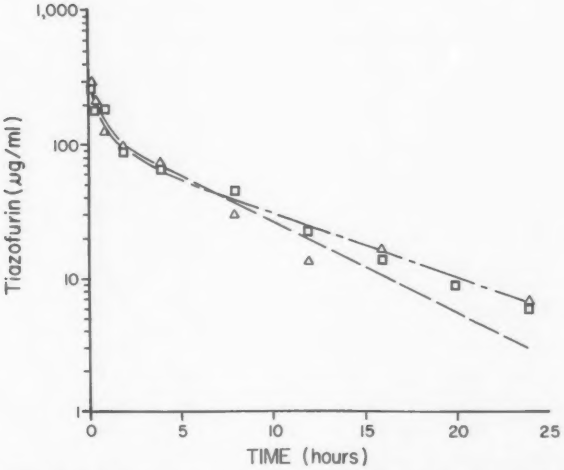

FIGURE 3.—Tiazofurin serum levels from Day 1 (△) and Day 5 (□) in a patient receiving 4100 mg/m^2/day × 5.

In three cases analyzed, 54%–93% of the Day-1 dose was recovered from the urine as unchanged drug within 24 hours. In all courses in which pharmacokinetics were evaluated, patients had normal renal function as estimated by initial serum creatinine values. Over the (limited) range of observed serum creatinine, there was no significant statistical correlation with β-half-time. Pharmacokinetic parameters as evaluated in 15 courses in 13 patients did not have apparent predictive value for toxic effects, although the small sample size and the complex nature of toxicity render any conclusion premature. Pharmacokinetic samples were not obtained from two patients experiencing dose-limiting toxic effects at the highest dose of 4100 mg/m^2/day.

Antitumor Activity

No tumor responses were observed in the course of this trial.

DISCUSSION

Tiazofurin when administered by iv bolus daily for 5 days (often with concurrent allopurinol) was poorly tolerated due to multiple toxic effects, especially headache, nausea, emesis, lethargy, and myalgia. These reversible and apparently nonthreatening effects frequently led to discontinuation of drug treatment. Although these acute effects were most severe at the highest doses, the frequency of treatment interruption was not markedly different at 4100 than at 1100 mg/m^2/day. This renders recommendation of a dose for this schedule in phase II trials problematic. Use of a moderate or high dose may unfavorably prejudice phase II trials, as a high proportion of patients predictably will not complete the planned 5-day course of treatment. A significant incidence of treatment interruption is probable with any dose ≥ 1100 mg/m^2/day. A reasonable dose for phase II trials, then, may be between 550 and 1000 mg/m^2/day. Although this study evaluated dose events significantly higher than those in other studies, our recommended phase II dose is somewhat lower, as is apparent from inspection of table 8.

The use of such a modest, nonmyelotoxic dose could be criticized on the basis that significant, dose-dependent antitumor activity could be missed. The preclinical evidence for a steep dose-response curve for tiazofurin

TABLE 8.—Tiazofurin: dose evaluations from phase I studies

Author (ref No.)	Schedule	Dose (mg/m^2/day)* MTD	RECD
Roberts et al (present study)	Daily × 5 (10-min infusion)	3300	550–1000
Melink et al (12)	Daily × 5 (30-min infusion)	1650	1100
Balis et al (13)	Daily × 5 (10-min infusion)†	2200†	2200†
Batist et al (14)	Continuous infusion	1100–1450	—
Raghavan et al (16)	Continuous infusion	1650	1500
Trump et al (15)	Continuous infusion	< 900	Too toxic

*MTD = maximum tolerated dose; RECD = recommended dose for phase II evaluation.
†Pediatric age group only.

antitumor activity is equivocal. A significant dose response was apparent in the treatment of ip implanted L1210 leukemia with tiazofurin administered ip daily × 5, but no clear dose response emerged in the treatment of iv implanted Lewis lung carcinoma with an ip daily × 9 schedule (1,3).

The apparent difficulties for phase II evaluation of a daily × 5 schedule using high doses may lead to consideration of other schedules in which intermittent administration of higher doses might be better tolerated. This approach would be subject to criticism, however, as tiazofurin activity may be schedule dependent. In L1210 leukemia treated at optimal doses, repeated daily administration for 5 or 9 days is superior to a single dose (1,3).

Even low doses of tiazofurin cause significant alterations of purine metabolism. In this trial significant elevations of serum uric acid and urine uric acid excretion were prevented or controlled by administration of allopurinol. This approach may have contributed to the absence of toxic effects of uric acid precipitation such as acute renal failure or acute gouty arthritis. Coadministration of tiazofurin and allopurinol did result, however, in increased serum levels and urine excretion of xanthine and hypoxanthine. Whether altered purine catabolism contributed to observed toxic effects is unknown.

Although limited evaluation utilizing the P388 tumor model suggests that coadministration of allopurinol has no impact upon the antitumor efficacy of tiazofurin, extensive testing of this hypothesis has not been reported (1). The possibility that interactions between these compounds affect antitumor activity and toxicity remains, and further investigation may be warranted. In the interim, we recommend that in phase II trials either allopurinol administration should be routine or else uric acid should be monitored on a daily basis during treatment.

One case each of pericarditis and fatal cardiomyopathy were observed in this trial. These two events in eight courses initiated at 4100 mg/m^2/day indicate that this is not an acceptable dose.

Skeletal muscle toxicity, both symptomatic and asymptomatic, was frequent. Reversible leukopenia and thrombocytopenia were observed, although this was not dose limiting. The unexpected incidence of symptomatic anemia suggests that a specific erythroid toxicity may be present, although this hypothesis cannot be evaluated adequately on the basis of data from this trial.

No useful correlates with toxicity other than dose emerged from this study. For many parameters of interest, of course, the sample size is inadequate. As mentioned, patients with prior cytotoxic chemotherapy appear to experience more profound myelotoxicity with tiazofurin. The small sample size, the variable and only moderate degree of myeloid toxicity observed, and the fact that no patients treated at the highest doses had received extensive prior chemotherapy render this conclusion tentative. Also as noted, coadministration of allopurinol had no apparent impact upon toxic effects (other than alterations in purine metabolism). Alonso et al (23) have reported that acute deterioration in renal function occurring in some patients during treatment, presumably due to tiazofurin, is associated with increased myelotoxicity. As we did not monitor serum creatinine during treatment, we cannot comment directly upon this point. In our study during observation after treatment, creatinine elevations > 0.2 mg/dl occurred in four of 30 courses; in three cases the abnormality was transient and not clearly related to drug administration; in one, it probably was related to the underlying disease. Batist et al (14) observed increased nonmyeloid toxicity in two patients with compromised or deteriorating renal function treated by 5-day continuous infusion. In our study only two courses were initiated with baseline abnormal serum creatinine values (1.6 mg/dl in each case); neither course was completed due to toxicity and patient intolerance. We do not believe that conclusions can be drawn from our experience.

Tiazofurin disposition observed in this trial was similar to that observed in preclinical studies in mammals. Arnold et al (11) reported that the disposition of tiazofurin in mice, rats, rabbits, and dogs best fit a three-compartment open model with first-order elimination. The first phase determined by this model corresponded to changes in plasma levels determined from multiple samples taken during the first 2 minutes following rapid iv push drug administration; corresponding data points were not observed in this study. The γ phase half-time reported by Arnold et al, which for dogs ranged from 3.4 hours at 250 mg/m^2 to 6.5 hours at 4000 mg/m^2, is similar to the corresponding β phase of 4.2 hours in this study. In mice, rats, dogs, and humans the primary route of elimination is urinary excretion, with most administered drug recoverable from the urine, unaltered, within 24 hours. In animals and humans the apparent volume of distribution by area exceeds total body water. This is consistent with significant tissue binding of drug. It is important to note that, in this study, pharmacodynamics of the presumed active metabolite, tiazofurin adenine dinucleotide, have not been evaluated.

Despite extensive preclinical investigations, the protean toxicities of tiazofurin cannot be understood in terms of known metabolic effects. Although much may be learned by further clinical trials, a better understanding of mechanisms of activity and toxicity perhaps would promote a more rational approach to future clinical investigations.

REFERENCES

1. O'DWYER PJ, SHOEMAKER DD, JAYARAM HN, ET AL. Tiazofurin: a new antitumor agent. Invest New Drugs 2:79-84, 1984.
2. KOVACS G, SIMONIDESZ V, TOMOSKOZI I, ET AL. 2-β-D-Ribofuranosylthiazole-4-carboxamide, a novel potential antitumor agent for lung tumors and metastases. J Med Chem 25:107-108, 1982.
3. Clinical Brochure. Tiazofurin. Bethesda, MD, National Cancer Institute, Dec 1982.
4. LEE H, PAWLAK K, NGUYEN BT, ET AL. Biochemical differences among four inosinate dehydrogenase inhibitors, mycophenolic acid, ribavirin, tiazofurin, and selenazofurin, studied in mouse lymphoma

cell culture. Cancer Res 45:5512-5520, 1985.

5. COONEY DA, JAYARAM HN, GEVEYEHU G, ET AL. The conversion of 2-β-D-ribofuranosyl-thiazole-4-carboxamide to an analogue of NAD with potent IMP dehydrogenase-inhibitory properties. Biochem Pharmacol 31:2133-2136, 1982.
6. STREETER DG, and ROBINS RK. Comparative in vitro studies of tiazofurin and a selenazole analog. Biochem Biophys Res Commun 115:544-550, 1983.
7. SWEENEY MJ, HOFFMAN DH, and ESTERMAN MA. Metabolism and biochemistry of mycophenolic acid. Cancer Res 32:1803-1809, 1972.
8. SMITH CM, FONTENELLE LJ, MUZIK H, ET AL. Inhibitors of inosinate dehydrogenase activity in Ehrlich ascites tumor cells in vitro. Biochem Pharmacol 23:2727-2735, 1974.
9. NELSON JA, ROSE LM, and BENNETT LL, JR. Mechanism of action of 2-amino-1,3,4-thiadiazole (NSC-4728). Cancer Res 37:182-187, 1977.
10. BERGER NA, BERGER SJ, CATINO DM, ET AL. Modulation of nicotinamide adenine dinucleotide and poly(adenosine diphosphoribose) metabolism by the synthetic "C" nucleoside analogs, tiazofurin and selenazofurin. J Clin Invest 75:702-709, 1985.
11. ARNOLD ST, JAYARAM HN, HARPER GR, ET AL. The disposition and metabolism of tiazofurin in rodents, rabbits and dogs. Drug Metab Dispos 12:165-173, 1984.
12. MELINK TJ, VON HOFF DD, KUHN JG, ET AL. Phase I evaluation and pharmacokinetics of tiazofurin (2-β-D-ribofuranosylthiazole-4-carboxamide, NSC-286193). Cancer Res 44:2859-2865, 1985.
13. BALIS FM, LANGE BJ, PACKER RJ, ET AL. Pediatric phase I trial and pharmacokinetic study of tiazofurin (NSC-286193). Cancer Res 45:5169-5172, 1985.
14. BATIST G, KLECKER RW, JR, JAYARAM HN, ET AL. Phase I and pharmacokinetic study of tiazofurin (TCAR, NSC-286193) administered by continuous infusion. Invest New Drugs 3:349-366, 1986.
15. TRUMP DL, TUTSCH KD, KOELLER JM, ET AL. Phase I clinical study with pharmacokinetic analysis of 2-β-D-ribofuranosylthiazole-4-carboxamide (NSC-286193) administered as a five-day infusion. Cancer Res 45:2853-2858, 1985.
16. RAGHAVAN D, BISHOP J, SAMPSON D, ET AL. Phase I and pharmacokinetic study of tiazofurin (NSC-286193) administered by 5-day continuous infusion. Cancer Chemother Pharmacol 16:160-164, 1986.
17. ACKERLY CC, NEWMAN RA, and MCCORMACK JJ. A TLC-HPLC method for determination of tiazofurin (NSC-286193) in serum. J Liquid Chromatogr 6:1239-1247, 1983.
18. MERTZLER CM, and WEINER DL. PCNONLIN User's Guide. Statistical Consultants, Inc. 1984.
19. BOULIEU R, BORY C, and BALTASSAT P. High-performance liquid chromatographic determination of hypoxanthine and xanthine in biological fluids. J Chromatogr 233:131-140, 1982.
20. MIYAZAKI H, MATSUNAGA Y, YOSIDA K, ET AL. Determination of plasma and urinary uric acid, xanthine, hypoxanthine, allopurinol, oxipurinol, orotic acid, orotidine and creatinine by high-performance liquid chromatography. J Chromatogr 274:75-85, 1983.
21. BLAUCH MB, and KOCH FC. A new method for the determination of uric acid in blood and urine. J Biol Chem 130:443, 1939.
22. HENRY RJ, SOBEL C, and KIM J. A modified carbonate-phosphotungstate method for the determination of uric acid and comparison with the spectrophotometric uricase method. Am J Clin Pathol 28:152, 1957.
23. ALONSO MT, O'DWYER PJ, LEYLAND-JONES B, ET AL. Tiazofurin: myelosuppression at low doses relates to nephrotoxicity. Proc ASCO 3:35, 1984.

Phase II Trial of High-Dose Cytarabine and Cisplatin in Locoregional Previously Untreated Squamous Carcinoma of the Head and Neck: A Piedmont Oncology Association Study[1,2]

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Cytarabine (ara-C) has consistently exhibited marked synergistic cytotoxicity when combined with cisplatin (CDDP) in both in vitro and in vivo models. Studies by Bergerat et al (1) and Vadi and Drewinko (2) in a human colon carcinoma cell line (LoVo) have outlined the dose and schedule dependency of this interaction; the maximum effect was noted with concomitant drug administration (2) and was dependent on the ara-C concentration (increased effect with higher concentrations). Attempts to duplicate this effect in clinical trials have been largely unsuccessful, possibly due to the use of inadequate doses or to the heavily pretreated patient population studied (3-5). A phase I trial at our institution defined the maximum tolerated dose of ara-C in combination with bolus CDDP (100 mg/m^2) to be 3 g/m^2 when administered as a 3-hour infusion (6). Since previous phase II studies of the combination employed much lower ara-C doses in heavily pretreated patients, we instituted a phase II trial of this combination in patients with previously untreated squamous carcinoma of the head and neck, a CDDP-responsive disease, to test the potentiation of CDDP by ara-C.

PATIENTS AND METHODS

Only patients with histologically documented squamous carcinoma of the head and neck confined to the primary site and regional lymph nodes by clinical staging (chest x-ray, physical examination, and serum chemistries) who had received no prior surgery, radiotherapy, or chemotherapy were entered. Other eligibility requirements included a Zubrod performance status of 0-2; measurable disease; adequate hepatic, renal, and bone marrow functions; and signed protocol-specific informed consent. All patients were seen prior to chemotherapy by a head and neck surgeon and radiotherapist for appropriate prechemotherapy tumor mapping in anticipation of definitive local therapy after completion of chemotherapy.

Treatment consisted of CDDP (100 mg/m^2 iv) over 30 minutes followed by ara-C (3 g/m^2) over 3 hours every 3 weeks for a maximum of three courses. Hydration included $>$ 4 hours of 5% dextrose in 0.45 normal saline (D5/0.45 NS) with 20 mEq of KCl and 8 mEq of $MgSO_4$/L at $\geq$ 125 ml/hour, 500 ml of D5/0.45 NS over 30-60 minutes just prior to CDDP, and another 500 ml with CDDP and 500 ml over 1 hour after CDDP, followed by resumption of D5/0.45 NS with KCl/$MgSO_4$ at 125 ml/hour until the next morning. Dose modifications for myelotoxicity were not made; if the wbc count was $<$ 3000/mm^3 or the platelet count was $<$ 100,000/mm^3 on the day of therapy, treatment was withheld for 1 week. If recovery to the above levels occurred after 1 week, full doses of each drug were administered; if recovery had not occurred, the patient was removed from the protocol. Modification for nephrotoxicity was made for a creatinine of 1.6-2.0 mg/dl (50% CDDP dose) or $>$ 2.0 mg/dl (therapy resumed in 1 week at 50% CDDP dose if recovery to $<$ 2.0 mg/dl; off study if not $<$ 2.0 mg/dl).

Patients were examined by the initial head and neck surgeon after each course of therapy. Patients with progressive disease after one course or stable disease after two courses were considered treatment failures and proceeded to definitive therapy. All other patients received three courses of therapy unless removed from the study because of toxicity. Standard World Health Organization response criteria were used.

RESULTS

Ten patients were entered between August 1985 and January 1986, all of whom were evaluable. The pretreatment patient characteristics, response data, and toxic effects are shown in table 1. One of ten patients

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TABLE 1.—Patient characteristics, response, and toxicity

Characteristic	No. of patients
Entered	10
Evaluable	10
Median age in yrs (range): 56 (50–69)	
Zubrod performance status	
1	7
2	3
Sex	
Male	5
Female	5
Primary tumor site	
Oropharynx	3
Hypopharynx	3
Oral cavity	2
Larynx	2
Nodal status	
N0	1
N2a	2
N2b	4
N3b	3
Stage	
3	1
4	9
Response	
Complete	0
Partial	1
Toxicity*	
Renal	
Grade 3	1
Grade 4	0
Hematologic	
Grade 3	2
Grade 4	1
Treatment-related death	3†

*World Health Organization scale.

†2 with refractory hypotension posttherapy; 1 with neutropenia-related sepsis.

responded; there were no complete responses (response rate, 10%; 95% confidence interval, 0.25%–44%). Five patients received three courses of therapy, two received two, and three received only one. Toxicity was severe, with three treatment-related deaths: one from neutropenia-related sepsis and two from unexplained refractory hypotension with subsequent renal failure which developed within 24 hours of treatment. The latter patients were unresponsive to fluids and vasopressors; sepsis and myocardial dysfunction were excluded in both by appropriate laboratory studies. There was no evidence of renal damage or other long-term toxicity in patients who received three courses. Although initial design called for accrual of at least 14 patients, the study was closed early in view of the response rate and lethal toxicity in this potentially curable patient population.

DISCUSSION

The transfer of laboratory investigation to clinical trials is the ultimate goal of laboratory investigation of drug-drug interactions in cancer chemotherapy. Unfortunately, it is impossible to determine what in vivo drug concentrations are needed to duplicate in vitro observations. In the case of the ara-C:CDDP interaction, maximal effects in vitro were observed with an ara-C concentration of 1000 μg/ml in conjunction with CDDP at 10 μg/ml. At CDDP levels ≤ 3 μg/ml or ara-C levels ≤ 200 μg/ml, minimal effects were noted. Comparable drug levels can be achieved for only brief time periods in humans (6,7). Since dose-response effects appear to be more dependent on the ara-C dose in vitro, our phase I trial focused on the maximum tolerated dose of ara-C that could be added to a fixed dose of CDDP that would achieve plasma levels ≥ 3 μg/ml (7). Three grams per meter-squared of ara-C over 3 hours was the highest dose that when combined with this CDDP dose resulted in reversible toxicity. This dose of ara-C resulted in sustained plasma levels of only 10–50 μg/ml (6). It is possible that further escalation of the ara-C and/or CDDP doses would have yielded synergistic cytotoxicity but the results of our phase I trial suggest that higher doses would have produced unacceptable toxicity with this schedule (6).

As described in this report, results with this combination in a disease responsive to CDDP were dismal, with a response rate of 10% (95% confidence intervals, 0.25%–44%). The response rate to CDDP in previously untreated patients with squamous cell carcinoma of the head and neck is 40%–70% (8). Despite the very small number of patients, this study demonstrates that the likelihood of ara-C potentiating CDDP in patients with squamous carcinoma of the head and neck is negligible with this or a similar schedule. In addition, the combination resulted in prohibitive toxicity not noted with either when administered as a single agent. Of particular note are the two cases of refractory hypotension developing within 24 hours of therapy, which resulted in subsequent renal failure and death despite appropriate supportive care. Although the mechanism is unknown, it is similar to the adrenergic toxicity noted with cyclocytidine in experimental situations (9). In view of these findings, further investigation of this combination of ara-C and CDDP in this dose and schedule in this group of patients cannot be justified.

REFERENCES

1. BERGERAT JP, DREWINKO B, CORRY P, ET AL. Synergistic lethal effect of *cis*-dichlorodiammineplatinum(II) and 1-β-D arabinofuranosyl cytosine. Cancer Res 41:25–30, 1981.
2. VADI H, and DREWINKO B. Kinetics and mechanism of the 1-β-D-arabinofuranosyl-induced potentiation of *cis*-diamminedichloroplatinum(II) cytotoxicity. Cancer Res 46:1105–1109, 1986.
3. SCHILSKY R, GREEN M, and ANDERSON J. Cytarabine-cisplatin interactions in patients with advanced cancer. Semin Oncol 12(suppl 3):171–176, 1985.
4. BERNSTEIN J, JACOBS C, MEYERS F, ET AL. A phase II study of cisplatin and cytosine arabinoside for recurrent squamous cell carcinoma of the head and neck. Am J Clin Oncol 9:58–60, 1986.
5. KEENEY ED, FREEDMAN RS, DREWINKO B, ET AL. Clinical evaluation of high-dose cytarabine and cisplatin in recurrent cervical carcinoma. Cancer Treat Rep 69:1023–1025, 1985.

6. MUSS H, CAPIZZI R, ATKINS J, ET AL. Phase I trials of high-dose cytosine arabinoside (HDara-C) and HDara-C plus cisplatin in patients with advanced malignancies. Semin Oncol 12(suppl 3):166–170, 1985.
7. BELT RJ, HIMMELSTEIN KJ, PATTON TF, ET AL. Pharmacokinetics of non-protein-bound platinum species following administration of *cis*-dichlorodiammineplatinum(II). Cancer Treat Rep 63:1515–1521, 1979.
8. ERWIN T, CLARK J, and WEICHSELBAUM R. Multidisciplinary treatment of advanced squamous carcinoma of the head and neck. Semin Oncol 12(suppl 6):71–78, 1985.
9. BURKS T, LOO T, and GRUBB M. Mechanism of the cardiovascular actions of cyclocytidine. Proc Soc Exp Biol Med 159:374–379, 1978.

Phase I and Pharmacokinetic Study of *trans*-$N_3P_3Az_2(NHMe)_4$[1]

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***trans*-$N_3P_3Az_2(NHMe)_4$, an aziridinyl-substituted cyclophosphazene, was tested for its toxicity, pharmacokinetic behavior, and cytostatic activity in a phase I study in 30 patients. A total of 66 courses of a single iv bolus injection were given in five dose steps. Toxicity consisted of leukocytopenia and thrombocytopenia, dose limiting at 70 mg/m^2, mild anemia, and some nausea. Leukocyte and platelet count nadirs fell between 2 and 3 weeks, with recovery at 6 weeks. A tendency for cumulative thrombocytopenia was noticed in three of 13 patients at risk. A three-phase plasma elimination model was applicable with $t\frac{1}{2}\alpha$ of 9.9 minutes, $t\frac{1}{2}\beta$ of 78.5 minutes, and $t\frac{1}{2}\gamma$ of 435.5 minutes; renal drug excretion was substantial. Three partial remissions in 21 evaluable patients suggest some clinical activity for this drug. [Cancer Treat Rep 71:155–159, 1987]**

trans-$N_3P_3Az_2(NHMe)_4$ (AZP) belongs to the aziridinyl-substituted cyclophosphazenes. This group of agents has a wide spectrum of activity both in vitro and in vivo (1,2). The aziridinyl groups are probably responsible for the cytostatic activity of the compounds, but the exact mode of action on the DNA is different for the various compounds and is probably determined by the carrier ring structure (3).

In preclinical studies, AZP gave an increase in life span of 113% in L1210 bearing mice after a single ip injection of the maximally tolerated dose. Of these animals, 30% were cured. In vivo activity was also found against B16 melanoma and mouse osteosarcoma. In vitro activity against human small cell lung cancer cell lines was found in our laboratory (3). In mice, the dose that killed 10% of the animals (LD10) after a single ip injection was 100 mg/m^2.

Clinical studies with another member of this group, SOAz, revealed some cytostatic activity, but with cumulative and irreversible bone marrow aplasia (4,5). Further preclinical studies indicated that this side effect of SOAz could also be demonstrated in mice, and occurred especially after repeated daily injections. From a number of derivatives tested in these studies, AZP had the least cumulative marrow toxicity (6). We therefore selected this agent for further clinical studies.

PATIENTS AND METHODS

Patient Selection

Selection criteria for patients to be entered in this study were that they should have histologically confirmed malignant disease, not amenable to known effective treatment regimens, and progression of signs or symptoms caused by the tumor. Patient age was between 21 and 75 years; life expectancy had to be at least 2 months, and the performance status according to the World Health Organization (WHO) criteria should be better than 3. No anticancer treatment could have been given during the last 3 weeks before entry (6 weeks for nitrosoureas and mitomycin). Patients were required to have adequate bone marrow function (defined as leukocyte count $\geq 4.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L), adequate renal function (serum creatinine ≤ 120 μmols/L and/or creatinine clearance ≥ 50 ml/minute), and adequate liver functions (serum bilirubin ≤ 20 μmols/L). Informed consent was obtained according to the Helsinki declaration. The study was approved by the local Medical Ethical Committee.

Drug Synthesis and Administration

AZP was synthesized by the Department of Inorganic Chemistry of the State University of Groningen. The

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Netherlands. The required amount of drug for infusion was reconstituted with 10 ml of 0.9% NaCl solution. The drug was administered as a push injection iv on Day 1 (one course). Subsequent courses were planned to be given after at least 3 weeks or after full recovery of toxicity, and only in the absence of progression of signs or symptoms due to the disease.

Dose Schedule

The starting dose was established at 10 mg/m^2, corresponding to one-tenth of the LD10 in mice. Subsequent dose escalations were carried out according to the modified (7) Fibonacci scheme (10, 20, 33, 50, and 70 mg/m^2). A minimum of three patients were treated at each dose level if no toxicity occurred, otherwise the minimum was six patients. No dose escalations were carried out in individual patients.

Study Parameters and Criteria

Before treatment the complete medical history was assessed, and physical examination was performed with documentation of metastatic disease and objective tumor measurement, if possible. Laboratory studies included a cbc, blood chemistry (SMAC 16), urine analysis, electrocardiogram, and chest roentgenograms. Blood cell count and chemistry were repeated twice weekly, and physical examinations, electrocardiogram, and chest roentgenograms were repeated once weekly during at least 3 weeks after the last drug administration.

Toxicity was recorded according to the WHO grading system (0–IV) (8). In patients with measurable or evaluable disease, tumor response was assessed according to the following criteria. Partial remission was defined as a reduction by at least 50% of the sum of the products of the two largest perpendicular diameters of all measurable disease for at least 4 weeks without the appearance of new lesions. Stable disease was defined as a $<$ 50% reduction or a $<$ 25% increase of the measurable tumor mass for at least 4 weeks without new lesions. Duration of response was determined from the start of the therapy until the moment of disease progression.

End point of the study was the occurrence of grade IV hematological toxicity or grade III extramedullary toxicity in two patients of a dose step.

Pharmacokinetics

Nine patients were studied during their first course. Two of them were treated with 33 mg/m^2, three with 50 mg/m^2, and four with 70 mg/m^2. In all patients, serum samples were drawn at: 0, 5, 10, 15, 20, 30, 45, 60, and 90 minutes and at 2, 3, 4, 6, 8, 12, 18, and 24 hours past injection. Samples were immediately centrifuged and frozen.

Urine was collected during 24 hours after drug infusion, and alkalinized by adding sodium bicarbonate to the collection bowls.

Assay

AZP was determined with a modification of the method described for the detection of SOAz (9). To 0.5 ml of serum or 1:5 with water-diluted alkalinized urine, 25 μl of sodium hydroxide (4 M) and 50 μl of a solution containing 100 mg SOAz/L in methanol were added. This mixture was extracted with chloroform. After centrifugation, the organic layer was evaporated at ambient temperature under vacuum. The residue was dissolved in 50 μl of methanol, and 1 μl was injected into a gas chromatograph with a 3.3-m (0.225-mm inside diameter), wall-coated open tubular capillary fused silica column (Chrompack BV, Middelburg, The Netherlands). For the detection, a model 18789A N-P-FID thermionic detector (Hewlett Packard Co, Avondale, PA, USA) was used. The detection limit in plasma of AZP was 0.005 mg/L; in urine, 0.04 mg/L. The coefficient of variation for both the serum and the urine determination is 5.0%.

Analysis of Pharmacokinetic Data

The plasma concentration time data for each patient were subjected to pharmacokinetic analysis using a DEC system 10 computer. The program includes a correction for infusion time (10), a statistical analysis comparing the accuracy of models containing different numbers of phases (11). Equations for distribution constants, elimination constants, total body clearance, and apparent central and peripheral distribution volumes have been described (12).

RESULTS

Toxicity

A total of 30 patients were entered in this trial; characteristics are given in table 1. A total number of 66 courses was administered. All patients were evaluable for toxicity. No drug-related deaths occurred. Extramedullary toxicity was restricted to mild nausea and sporadic vomiting, maximally, WHO grade II. This occurred in none of the 18 courses of the two lowest dose steps, in 13 of 21 (62%) in the third dose step, in five of 13 (38%) in the fourth dose step, and in five of 14 (36%) in the highest dose step. No other types of extramedullary toxicity were seen; specifically, no alopecia occurred.

Anemia, defined as a drop in hemoglobin level of 2 g/100 ml over a 3-week period following an AZP injection (in the absence of hemolysis or blood loss), was seen once in the two lowest dose levels, and four times in both the 33 mg/m^2 and the 50 mg/m^2 levels. A total of 50% of the 14 courses at the highest level were accompanied by anemia. Transfusion was never required.

Leukocytopenia, and especially thrombocytopenia, were the dose-limiting toxic effects at the 70 mg/m^2 dose level. These hematological toxic effects are shown in table 2.

The patients who experienced grade II and III leukocytopenia or thrombocytopenia at a dose level of 33 mg/m^2

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Entered	30
Evaluable for toxicity	30
Evaluable for response	21
Male/female	19/11
Median age in yrs (range): 58 (26–72)	
Median performance status (range): 1 (0–2)	
Tumor type	
Small cell lung carcinoma	5
Non-small cell lung carcinoma	10
Gastrointestinal	4
Ovarian carcinoma	3
Adenocarcinoma, primary unknown	4
Melanoma	2
Renal carcinoma	1
Soft tissue (leiomyosarcoma)	1
Prior treatment	
None	8
Limited	11
Extensive*	11

*Extensive therapy is defined as treatment with ≥ 2 drugs for > 3 mos, or cytostatics and radiotherapy, or radiation therapy on > 2 locations.

had received extensive pretreatment. No indications for cumulative myelosuppression were found in six patients who received repeated courses at this dose level, since the level of nadirs and the speed of recovery remained unchanged in subsequent courses. All courses could be given with 3-week intervals at this dose level.

At a dose level of 50 mg/m^2, the occurrence of leukocytopenia and thrombocytopenia was independent of the prior therapy. One of four patients who received repeated courses had lower nadir values and a slower recovery in the second and third than in the first course (table 3). Recovery of leukocyte count and platelet count level was complete in 4–6 weeks at this dose level.

No correlation between the occurrence of toxicity and the extension of prior therapy could be established at a dose level of 70 mg/m^2. Normal hematological values were reached 6 weeks after injection, with the exception of one patient who took 10 weeks to recover.

Cumulative myelosuppression was strongly suggested (table 3) by the fact that in two of the three patients who received repeated courses at the 70 mg/m^2 level, lower nadir values and a slower recovery were seen.

Response

A total of 21 patients were evaluable for response. Three partial responses were seen. Two patients with a poorly differentiated squamous cell bronchial carcinoma had a partial response of lung lesions, lasting 14 and 16 weeks, respectively, and one patient with a renal carcinoma showed a partial response of lung metastases lasting 14 weeks. The two patients with non-small cell lung carcinoma (NSCLC) had not received chemotherapy previously. The patient with renal carcinoma had received vindesine.

Ten patients with preexistent progression of signs or symptoms of disease were classified stable after two courses of AZP, and eight evaluable patients had disease progression. Of these ten patients with stable disease, three had NSCLC.

Clinical Pharmacology

Pharmacological data in individual patients are given in table 4. At the first dose level of 33 mg/m^2, the data fit a two-phase linear pharmacokinetic model, but at the

TABLE 2.—Hematological toxicity

			Leukocyte count		Platelet count	
Dose (mg/m^2)	No. of patients	No. of courses	Median nadir (range)*	Median Day of nadir	Median nadir (range)*	Median Day of nadir
10	3	5	7.8 (4.3–10.6)	22	246 (145–331)	15
20	3	13	5.2 (3.7–7.9)	7	159 (130–269)	10
33	7	21	4.9 (1.9–7.5)	18	149 (46–360)	17
50	7	13	3.8 (1.5–5.5)	20	162 (14–367)	16
70	10	14	3.2 (1.4–9.1)	21	97 (10–208)	14

*$\times 10^9$/L.

TABLE 3.—Indications for cumulative toxicity in 3 patients, A, B, and C

			Wbc/platelet count nadir values ($\times 10^9$/L)			Wbc/platelet count Day of recovery		
Patient	Pretreatment	Dose (mg/m^2)	1st course	2nd course	3rd course	1st course	2nd course	3rd course
A	Limited	50	3.8/174	2.6/53	2.0/14	27/13	35/28	50/50
B	None	70	1.5/27	1.6/10	—	28/28	43/71	—
C	None	70	3.9/136	2.3/123	4.6/42	38/16	35/8	35/35

TABLE 4.—Pharmacokinetic data*

Patient No.	Dose (mg/m^2)	Creatinine clearance (ml/min)	Total dose (mg)	$t_{1/2}\alpha$ (min)	$t_{1/2}\beta$ (min)	$t_{1/2}\gamma$ (min)	VC (L)	Vd^{ss} (L)	AUC $mg/min.L^{-1}$	Cl (ml/min)
1	33	111	63	10.0	62.4	—	7.4	11.5	399	145
2	33	125	58	9.0	91.1	—	8.4	17.9	395	160
3	50	118	83	15.2	68.1	246	11.4	18.4	724	114
4	50	193	77	8.4	70.2	288	8.5	20.1	506	152
5	50	52	100	14.0	96.5	474	11.4	37.0	819	122
6	70	82	120	5.7	76.8	771	7.2	57.0	1090	110
7	70	114	120	4.9	72.1	500	7.2	37.0	1020	118
8	70	106	119	17.3	79.2	—	15.3	21.0	568	210
9	70	146	116	5.4	90.1	334	7.2	18.7	953	122

*$t_{1/2}\alpha$, $t_{1/2}\beta$, and $t_{1/2}\gamma$ = 50% elimination time in α, β, and γ phase; VC = volume of central compartment; Vd^{ss} = apparent volume of distribution in steady state; AUC = area under the curve; and Cl = clearance.

higher dose levels in six of the seven patients a three-compartment model is superior. Otherwise, plasma pharmacokinetics seem to be dose independent. The mean $t_{1/2}\alpha$ for the whole group ($n = 9$) is 9.9 (SD, 4.2) minutes, mean $t_{1/2}\beta$ 78.5 (SD, 11.0) minutes ($n = 9$) and where appropriate ($n = 7$) $t_{1/2}\gamma$ is 436 (SD, 176) minutes. The volume of the central compartment is 9.3 (SD, 2.6) L, the apparent volume of distribution is 26.5 (SD, 13.5) L. The total body clearance of the drug is 139 (SD, 30) ml/minute. Urinary excretion could only be determined in four patients. In one patient (No. 6, table 4), who voided alkaline urine while on artificial enteral nutrition, a 60% renal excretion of the injected drug was found; a renal clearance of 66 ml/minute is calculated in this patient. In three other patients in whom urine was rapidly alkalinized after micturation, drug excretion fractions of 34.0%, 37.0%, and 30.0% were found, accounting for renal clearances of 54, 59, and 37 ml/minute, respectively, (Patients 1, 2, and 9, table 4).

DISCUSSION

The toxicity of AZP is virtually limited to bone marrow depression. Although nausea occurred in a number of patients, this side effect was only marginal. Thrombocytopenia is dose-limiting and was severe, grade IV, requiring platelet transfusion in one patient at the 50 mg/m^2 dose level and in two patients at the 70 mg/m^2 dose level. It is difficult to predict, since it occurred twice in nonpretreated patients and was not seen in a heavily pretreated patient after a 70-mg/m^2 dose.

Nadir bone marrow depression occurred between the second and third week after injection and recovered after 6 weeks. In three of seven patients in the two highest dose levels who received repeated courses, evidence occurred of lower platelet count nadirs and slower recovery after subsequent injection. Therefore, this drug probably has a tendency for cumulative bone marrow depression as was described for SOAz (4,5). The small number of patients in a phase I study permits no conclusion as to the degree of this risk. As this effect was not seen at the 33-mg/m^2 level, we chose this dose with an interval of 3 weeks for a phase II study in NSCLC, especially since a response was seen in NSCLC with that dose. In view of the two partial responses and three cases of stable disease in the eight evaluable patients with NSCLC, this agent should be tested in that disease, preferably in patients not previously treated.

The determination of AZP in biological fluids required some modifications of the procedure previously described for SOAz (7) as AZP has a substantially higher water solubility than SOAz. Therefore, another extraction method using chloroform instead of dichloromethane was applied. This difference in solubility may also be reflected in the different pharmacokinetic behavior of AZP as compared to SOAz. AZP pharmacokinetics was found to be fitted best in a three-compartment model, while a two-compartment model was sufficient for SOAz. The difference in the elimination pattern in the lowest dose group (33 mg/m^2), compared to the higher groups, is probably due to the fact that the level of detection of the assay is too high to permit the establishment of the third phase in the low-dose group.

Probably the degree of renal excretion of AZP is substantial. A patient producing alkaline urine excreted 60% of the drug unchanged; in the other three patients, immediate alkalinization of the urine outside of the body left approximately 30% of the drug detectable. In other patients no, or minimal, urinary drug excretion was detected, probably due to rapid, intravesical disintegration of the drug in the presence of a low pH.

Animal experiments (6) indicated that a regimen using single-day bolus injection with cyclophosphazenes gave the least risk of cumulative toxicity. In the phase I study described here, a dose of 33 mg/m^2 once every 3 weeks leads to minimal toxicity and may have cytostatic activity. Further clinical studies with AZP have been initiated in our institution.

REFERENCES

1. LAMBERTS HB, VAN DER MEER-KALVERKAMP A, VAN DE GRAMPEL JC, ET AL. Cytostatic activity of inorganic heterocycles in an in vitro screening system. Oncology 40:301-304, 1983.
2. LABARRE JF, SOURNIES F, CROS S, ET AL. New designs in inorganic ring systems as anticancer drugs. Antitumor activity of the

aziridino (ethylene-imino) derivatives $(NPAz_2)_2NSOX$ with X = F, Az, Ph. Cancer Lett 12:245-250, 1981.

3. ZIJLSTRA JG, DE JONG S, VAN DE GRAMPEL JC, ET AL. Different type of DNA damage caused by three aziridinyl substituted cyclophosphazenes in a human small cell lung carcinoma cell line. Cancer Res 46:2726-2729, 1986.
4. RODENHUIS S, MULDER NH, SLEIJFER DT, ET AL. Phase I clinical trial of $(NPAz_2)_2NSOAz$: "SOAz." Cancer Chemother Pharmacol 10:178-181, 1983.
5. RODENHUIS S, MULDER NH, SLEIJFER DT, ET AL. Phase I evaluation of SOAz (1,3,3,5,5 pentakis(aziridino)-1 λ^6,2,4,6,3 λ^5,5 λ^5thia-triaza-diphosphorine-1-oxide) in a weekly schedule. Eur J Cancer Clin Oncol 20:645-649, 1984.
6. MULDER NH, DE VRIES EGE, TIMMER-BOSSCHA H, ET AL. Bone marrow toxicity of cyclophosphazenes is related to their structure and the treatment schedule. Eur J Cancer Clin Oncol 22:195-198, 1986.
7. HANSEN HH, SELAWRY OS, MUGGIA FM, ET AL. Clinical studies with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosurea. Cancer Res 31:223-227, 1971.
8. World Health Organization. Handbook for reporting results of cancer treatment. WHO Offset Publication No. 48. Geneva, WHO, 1979.
9. BENEKEN GENAAMD KOLMER MH, RODENHUIS S, VAN DE GRAMPEL JC, ET AL. Determination of the antitumor agent SOAz (1,3,3,5,5 pentakis(aziridino)-1 λ^6,2,4,6,3 λ^5,5 λ^5thia-triazadiphosphorine-1-oxide) by a gas chromatographic assay suitable for pharmacokinetic studies in man. Cancer Chemother Pharmacol 10:170-173, 1983.
10. LOO JCK, and RIEGELMAN S. Assessment of pharmacokinetic constants from postinfusion blood curves obtained after iv infusion. J Pharm Sci 59:53-55, 1970.
11. BOXENBAUM HG, RIEGELMAN S, and ELASHOFF RM. Statistical estimations in pharmacokinetics. J Pharmacokinet Biopharm 2: 123-148, 1974.
12. GREENBLATT DJ, and KOCH WESER J. Drug therapy. Clinical pharmacokinetics I. N Engl J Med 293:702-705, 1975.

Phase II Study of Mitoxantrone and Cytarabine in Acute Myeloid Leukemia[1]

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Thirty-eight patients with acute myeloid leukemia (AML) were treated with mitoxantrone (Mto) combined with cytarabine (Ara-C). Five patients had received no previous treatment for acute myeloid leukemia, seven were refractory to treatment with standard first-line chemotherapy, eight had relapsed during treatment, and 18 had relapsed after treatment was stopped. Eleven of these relapses were early (within 6 months of stopping treatment). Mto was given for 5 days by iv bolus injection at a dose of 10 mg/m^2 to 12 patients and at 12 mg/m^2 to 26. Ara-C was given at a dose of 1 g/m^2 twice daily by a 2-hour infusion for 3 days to 37 patients. One patient received Ara-C at a dose of 500 mg/m^2 twice daily for 3 days. Toxicity was acceptable except for cerebellar toxicity in two patients, which was irreversible in one. Twenty-two patients (56%) achieved complete remission (CR), and four achieved partial remission (10%). Seventy-five percent of the patients who had relapsed during treatment and 58% of those who had relapsed after treatment was stopped achieved CR. Eleven patients remain in CR at a median time of 10 months (range, 3–17) after treatment. In five patients remissions have lasted > 1 year, one in a patient treated in second relapse and one in a patient treated in third relapse. Mto and Ara-C appear to be effective salvage therapy in acute myeloid leukemia and should be considered for incorporation into first-line induction regimens. [Cancer Treat Rep 71:161–163, 1987]

The treatment of patients with relapsed and refractory acute myeloid leukemia (AML) presents a major therapeutic challenge since reported prognosis in this group of patients is poor (1). The leukemic cells tend to be highly resistant to chemotherapy and the cumulative cardiotoxicity of the anthracyclines used during the initial induction phase limits their further use. Mitoxantrone (Mto) is an anthracenedione derivative chemically related to the anthracyclines but is said to lack the cardiotoxicity of the anthracyclines. Mto acts by DNA intercalation. Early phase II studies with Mto showed significant activity in AML without cardiotoxicity (2). Encouraged by these reports we began a phase II study of Mto and cytarabine (Ara-C) in AML at the Hammersmith and London Hospitals, London.

PATIENTS AND METHODS

Thirty-eight patients were treated between October 1984 and February 1986. These patients had TdT-negative AML. There were 19 women and 19 men. Two children 6 and 12 years of age were treated. The median age of the remainder was 40 years (range, 19–73). Five patients had not received any previous chemotherapy, eight were refractory to three courses of standard first-line treatment, and 25 had relapsed during or after treatment. First-line treatment included two courses of 3+10 DAT (50 mg/m^2 of daunorubicin by iv bolus on Days 1, 3, and 5, 100 mg/m^2 of Ara-C twice daily by 24-hour infusion for 10 days, and 75 mg/m^2 of 6-thioguanine orally twice daily for 10 days) followed by MAZE (*m*-AMSA, 5-azacitidine, and etoposide given at doses of 100 mg/m^2 daily for 5 days). According to protocol, if patients were in remission after one or two courses of first-line treatment, they received two or four further maintenance courses of either MAZE (Courses 3 and 5), daunorubicin at a dose of 50 mg/m^2 on Day 1 and Ara-C at a dose of 200 mg/m^2 by 24-hour infusion for 5 days (Course 4), or daunorubicin with Ara-C given at a dose of 1 g/m^2 twice a day for 3 days (Course 6). If patients showed no response to three courses of first-line treatment they were considered refractory. Of the 25 relapsed patients, seven had relapsed while receiving treatment (four after the third course; three after the fourth) and 18 had relapsed after treatment was stopped. Eleven of these latter relapses occurred within 6 months

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TABLE 1.—Results of treatment in 38 patients with AML

	No. of patients			
	CR	PR	Other*	Total
No previous treatment	4	—	1	5
No remission†	2	1	5	8
Relapse				
During treatment	6	1	—	7
After treatment (< 6 mos)	7	1	3	11
After treatment (> 6 mos)	3	1	3	7
Total	22	4	12	38
Type of AML				
AML with MDS‡	2	1	3	6
Secondary AML§	1	—	2	3
AML supervened on CMML¶	1	—	—	1

*Resistant disease, death from hypoplasia or infection.

†Refractory to 3 courses of first-line treatment.

‡1 patient had no previous treatment; 2 patients were refractory to 3 courses of first-line treatment; and 3 relapsed.

§1 patient had no previous treatment; 1 was refractory to 3 courses of first-line treatment; and 1 relapsed.

¶No previous treatment.

(early relapses) (table 1). One of the patients was in second relapse and one was in third. Six of the 38 patients had coexistent myelodysplasia (MDS); in a seventh patient AML supervened on chronic myelomonocytic leukemia (CMML) of long duration. Three other patients had received previous chemotherapy for Hodgkin's disease, T-acute lymphoblastic leukemia, and follicular lymphoma (secondary AML).

Twelve patients received Mto at a dose of 10 mg/m^2 daily by ½-hour infusion on Days 1-5 and Ara-C at a dose of 1 g/m^2 twice daily by 2-hour infusion. The next 26 patients received Mto at 12 mg/m^2; the dose of Ara-C was left unchanged. One elderly patient in the former group received Ara-C at a dose of 500 mg/m^2 instead of 1 g/m^2. Nineteen patients received one course of treatment, 16 received two courses, and two who achieved a partial response (PR) with two courses received a third course; however, complete response (CR) was not achieved with further courses of treatment. Three patients in CR who had HLA-identical related donors received cyclophosphamide and whole-body irradiation followed by bone marrow transplantation. One patient in CR received two consolidation courses of Ara-C at 5 mg/m^2 twice a day by sc injection for 3 weeks at 3-week intervals. Thirty-two patients (84%) did not receive any further chemotherapy after treatment with Mto and Ara-C.

CR was defined as a reduction in the marrow blast cell count to < 5%, with a return to normal of the peripheral blood cell count and normalization of clinical features. PR was defined as a reduction in the marrow blast cell count to 5%-25% or failure of normalization of clinical features despite return to normal of the peripheral blood cell count. Survival data were assessed on June 1, 1986. Cytochemical and monoclonal antibody studies were performed on all patients. Biphenotypic leukemias were not included in the study.

RESULTS

The results of treatment are shown in table 1. Twenty-two of the 38 patients achieved CR and four achieved PR. Two of eight patients whose leukemia had failed to respond to first-line treatment achieved CR. CR was achieved with one course of treatment in ten patients and with two courses of treatment in 12. Four of the nine patients whose leukemia was associated with MDS or secondary to cytotoxic drug therapy achieved CR, but these remissions were of short duration. However, a prolonged remission (> 1 year) was obtained in the patient with AML supervening on CMML. The median duration of CR to June 1, 1986, was 10 months (range, 3-17). Unmaintained remissions have lasted > 1 year in five patients, which includes one patient who received a bone marrow transplant 3 months after starting the treatment with Mto and Ara-C. Of the 26 patients who received Mto at a daily dose of 12 mg/m^2, two-thirds (17 patients) had remission but only one-third (four of 12) of those had remission who received 10 mg/m^2 daily. However, five of the 26 patients who received the higher dosage died from pancytopenia. This different response did not reflect an unequal distribution of patients who were older, had refractory or secondary AML, or had AML with MDS in the two groups. Three of the patients who achieved CR relapsed with CNS leukemia, two during treatment and one 6 months after the end of treatment.

Chemotherapy was relatively well-tolerated. However, all patients experienced nausea, vomiting, alopecia, and mucositis, and five developed severe pruritus and dryness of the skin (asteatosis) (3). The most serious complication was cerebellar damage which occurred in two patients and was permanent in one. Three patients had mild cardiotoxicity as shown by fluid overload, which responded to diuretic therapy. Hematologic toxicity was comparable to that of standard 3+10 DAT, but thrombocytopenia was more prolonged. The median duration of neutropenia (neutrophil count $> 500 \times 10^7/L$) was 17 days (range, 14-24) and of thrombocytopenia (platelet count $> 50 \times 10^9/L$) was 28 days (range, 20-47).

Seventeen of 22 patients with leukemia died, nine of whom had failed to respond to the treatment. These nine patients included five who were refractory to first-line treatment, one who relapsed during first-line treatment, and two who relapsed after first-line treatment was stopped. In the other eight patients, CR lasted for a median of 6 months (range, 3-8), but they subsequently died with relapsed leukemia; no further rescue attempts were made. One other patient died 36 hours from the start of treatment from the tumor lysis syndrome and one from diabetic ketosis 14 days after starting treatment. Two patients died in CR from infection. Eight of the nine patients whose AML followed previous cytotoxic therapy or was associated with MDS died, all with leukemia that had failed to respond to Mto and Ara-C (four with resistant disease; one after PR) or was in relapse (three).

DISCUSSION

Of 38 patients with untreated, refractory or relapsed AML treated with Mto and Ara-C, 56% achieved CR. However, results were poor in secondary AML and AML associated with MDS. In refractory AML, two of eight patients achieved a short-lived CR, suggesting that cross-resistance of Mto with the anthracyclines is not complete.

A possible dose response was observed in this study: 30% of the patients who received Mto at a daily dose of 10 mg/m^2 achieved CR, whereas 63% who received 12 mg/m^2 achieved CR. This different response did not reflect an unequal distribution of patient characteristics in the two groups. Toxic effects appeared to depend on the dosage of both Mto and Ara-C. The patients reported by Hiddeman et al (4) received 3 g/m^2 of Ara-C twice daily for 4 days together with Mto. CR was achieved in eight of 20 patients (40%), but a high incidence of toxic effects was reported. In contrast, Prentice (5), using a dose of 100 mg/m^2 of Ara-C daily for 7 days, achieved CR in four of eleven patients (38%), with a lower incidence of toxic effects. The 56% CR rate in our study suggests that the doses of both Ara-C and Mto used gave a better toxic/therapeutic ratio. The three patients who developed signs of cardiotoxicity may have been unduly susceptible because of previous treatment with anthracyclines. This regimen alone appears ineffective in eradicating occult CNS disease since three patients relapsed with CNS leukemia despite being in CR.

The Mto and Ara-C combination appears to be effective salvage therapy in relapsed AML. CR may be expected in about one-half of the patients, and the toxicity is not excessive in relation to the benefit conferred. Remissions have lasted > 1 year in five patients, four of whom received no other treatment after Mto and Ara-C. It appears therefore that this treatment has a role in the long-term control of relapsed AML. It is possible that its incorporation into intensive therapy protocols for first-line treatment might increase the proportion of long-term survivors.

REFERENCES

1. VAUGHAN WP, KARP JE, and BURKE PJ. Two-cycle timed-sequential chemotherapy for adult acute non-lymphocytic leukemia. Blood 64:975, 1984.
2. VAN ECHO DA, SHULMAN PN, FERRARI A, ET AL. A phase II trial of mitoxantrone (DHAD NSC-301739) in adult acute leukemia. Proc ASCO 1:132, 1982.
3. DHARMASENA F, CHU AC, GOLDMAN JM, ET AL. Mitoxantrone-induced asteatosis. Lancet 2:101, 1985.
4. HIDDEMAN W, KREUTZMAN H, LUDWIG WD, ET AL. Mitoxantrone and high-dose cytarabine in refractory adult acute myeloid leukaemia. Lancet 2:508–509, 1985.
5. PRENTICE HG. Novantrone in leukaemias. *In* Proceedings of the 1st UK Novantrone Symposium. Liphook, Media Medica, 1984, pp 62–76.

High-Dose Lymphoblastoid Interferon in Advanced Renal Cell Carcinoma: An Eastern Cooperative Oncology Group Study[1,2]

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This report describes a phase II Eastern Cooperative Oncology Group (ECOG) study of high-dose lymphoblastoid interferon (IFN α-n1) in 39 patients with measurable, advanced renal cell carcinoma. The original treatment plan was 30×10^6 units/m^2 (30 mU) of IFN α-n1 im daily × 10 days; treatments were repeated every 21 days. This dose and schedule proved intolerable, with none of seven patients able to complete > 10 days of therapy because of fever, lassitude, hepatic dysfunction, and myelosuppression. Patients were subsequently treated with the following regimen: 3 mU/m^2 on Day 1; 5 mU/m^2 on Day 2; 10 mU/m^2 on Day 3; and 20 mU/m^2 on Days 4–10. Thirty-three new patients received this regimen and two patients received this schedule after having received 30 mU/m^2. Using this second regimen, 30% of the patients were able to complete two cycles of treatment without dose reduction or interruption. Five patients (13%) had partial response (ECOG criteria) of measurable tumor. Median time to response was 140 days. Responses were documented in lung metastases in four patients and in a pelvic soft tissue mass in the fifth. Response rates and survival times are similar to those seen in prior ECOG phase II trials in advanced renal cell carcinoma. Eight of 39 patients are still alive > 2 years after beginning therapy. Only two of these patients had had an objective response, however. Such prolonged survival is more frequent than has been seen in previous ECOG studies. The relative contribution of patient selection and interferon therapy to this survival is uncertain. [Cancer Treat Rep 71:165–169, 1987]

Renal cell carcinoma (RCC) is a relatively common tumor which is often regionally advanced or metastatic when recognized. Little benefit is obtained with the use of standard systemic chemotherapy (1). Rare spontaneous regression of advanced disease and prolonged survival with metastatic disease have suggested that host biologic response might be important in controlling the progression of RCC. These features resulted in the evaluation of interferons soon after these compounds became clinically available. Several investigators have reported activity of α-interferon in RCC (2–8). Despite the fact that several series have demonstrated some activity of α-interferon, issues regarding optimal dose and schedule are unresolved.

This report describes the results of a phase II study of human lymphoblastoid interferon (IFN α-n1, Wellferon) conducted by the Eastern Cooperative Oncology Group (ECOG) in collaboration with the Burroughs Wellcome Company. The purpose of this study was to investigate the efficacy and toxicity of high-dose IFN α-n1 in patients with measurable, metastatic RCC. We chose to evaluate a high dose of IFN α-n1 because of preliminary reports suggesting the possibility that there may be a direct relationship between dose and response (9).

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MATERIALS AND METHODS

Patient Characteristics

Forty patients were entered in this trial. All patients were required to have histologic proof of RCC with recurrent or metastatic disease and a measurable lesion as an indicator of antitumor response. All patients had an ECOG performance status (PS) of 0, 1, or 2, and none had received prior cytotoxic therapy, hormonal therapy, or immunotherapy. All patients were required to have adequate bone marrow (wbc count $\geq$ 4000/mm^3, hematocrit $\geq$ 30%, and platelet count $\geq$ 100,000/mm^3), renal (serum creatinine $<$ 2.0 mg/dl), and hepatic (bilirubin $<$ 1.5 mg/dl and SGOT less than three times normal) functions. Patients with symptomatic cardiac disease (New York Heart Association Functional Class III or IV) were excluded as were patients with known sensitivity to neomycin or polymyxin B. All patients gave informed consent according to institutional and Food and Drug Administration guidelines.

Treatment

IFN α-n1 is a highly purified product extracted from the supernatant of bulk cultures of the Namalwa cell line. The clinical formulation is 85%-90% pure interferon prior to the addition of a stabilizer, human serum albumin (10). This study was designed to investigate the efficacy and toxicity of high-dose IFN α-n1 and was based on the suggestion of enhanced efficacy of higher doses of IFN α-n1 as reported by Rohatiner et al (9). Two schedules of drug were studied.

Schedule A (seven patients).—Patients received 30 $\times$ 10^6 units/m^2 (30 mU/m^2) of IFN α-n1 im daily for 10 days. Treatments were to be repeated every 21 days. Seven patients received this schedule and none were able to complete 10 days of therapy without dose reduction or interruption. Consequently, the dose and schedule were modified to improve tolerance. All subsequent patients received this modified dose and schedule (Schedule B).

Schedule B (33 patients).—IFN α-n1 was administered im as follows: 3 mU/m^2 on Day 1, 5 mU/m^2 on Day 2, 10 mU/m^2 on Day 3, and 20 mU/m^2 on Days 4-10. Treatments were repeated every 21 days.

Before each injection, patients received acetaminophen at a dose of 650 mg orally; this was repeated every 4-6 hours for two or three doses. Patients were to receive 24 weeks (eight cycles) of therapy if treatment was tolerated and the disease was stable. Patients with stable or responding disease after 24 weeks were to continue receiving a maintenance regimen of 3 mU/m^2 three times weekly, for a total of 12 months of therapy. After 1 year therapy was discontinued. Two patients, however, continued therapy for $>$ 1 year.

Tumor Response and Dose Modification

ECOG criteria for response and toxicity were employed (11). In patients with grade 2 hematologic (granulocyte count, 500-1000/mm^3, platelet count, 50,000-75,000/mm^3) or neurologic ($>$ 2-level decline in PS) toxicity, uncontrolled fever ($>$ 39.7°C), severe rigors, or gastrointestinal (intractable vomiting) toxicity, the dose was reduced to 10 mU/m^2. Grade 3 hematologic, neurologic, or grade 4 gastrointestinal toxicity mandated cessation of the treatment cycle. Subsequent cycles were administered at 10 mU/m^2.

RESULTS

Patient Characteristics

Table 1 shows patient characteristics. Most patients were ambulatory (79%) and 54% began therapy within 6

TABLE 1.—Patient characteristics (n = 40)

Characteristic	% of patients
Age (yrs)	
$<$ 60	54
60-69	36
$\geq$ 70	10
Median: 59.0	
Range: 25-81	
Sex	
Male	64
Female	36
Initial PS	
Ambulatory (PS 0.1)	79
Nonambulatory (PS 2)	21
Time from initial diagnosis to on study	
$\leq$ 6 mos	54
$>$ 6 mos-$\leq$ 1 yr	21
$>$ 1 yr	26
Mean (mos): 17.9	
Median (mos): 4.0	
Range (mos): 0-132.2	
Prior nephrectomy	
No	28
Yes	72
Weight loss in previous 6 mos	
None	46
Some	51
Unknown	3
Lung metastases	
No	13
Yes	87
No. of cycles of therapy*	
1	26
2	15
3	15
4	21
$>$ 4	23
Mean: 3.6	
Median: 3	
Range: 1-10	
Cumulative dose ($\times$ 10^6 units/m^2)	
Mean: 393	
Median: 364	
Range: 28-1252	

*Induction step only. 7 patients received 1-71 weekly cycles of maintenance therapy.

months of the initial diagnosis of RCC. Eighty percent of the patients had lung metastases which served as the measurable marker for tumor response. On analysis of the trial one patient was found to have begun therapy with a hematocrit of 28% and was therefore considered ineligible. This patient began therapy on Schedule A, could not tolerate treatment, and was withdrawn from study after 7 days. This patient is excluded from the analyses which follow. Eighteen patients were entered at the University of Wisconsin, 15 at Rush-Presbyterian-St. Luke's Medical Center, three at Rochester and Minnesota, and one at Albany.

Toxicity

Schedule A (30 mU/m^2/day × 10)

Seven patients were entered at this dose and none were able to complete > 10 days of therapy without dose reduction or interruption. The following toxic effects necessitated treatment interruption before the completion of 10 days of therapy: (*a*) decline in PS of two or more levels (ECOG criteria), five patients; (*b*) SGOT elevation more than five times baseline (range of peak, 94–575 IU), five patients; and (*c*) uncontrollable fever > 39.7°C, five patients. One patient refused therapy after only one injection of 30 mU/m^2 because of hyperpyrexia and constitutional symptoms; three received five injections, two received eight injections, and one received a full 10-day course before prohibitive toxicity developed.

Mild leukopenia (median, 2.0×10^3 cells/mm^3; range, 1.3–4.9) occurred in these patients. Substantial percentage decrements in platelet count occurred with treatment (median decrease, 56%; range, 31%–71%); however, platelet counts $< 100{,}000$/mm^3 were recorded in only two patients (81,000 and 95,000/mm^3). Four patients continued on this schedule of therapy at a dose of 20 mU/m^2/day × 10.

Schedule B

Thirty-three patients were treated with IFN α-n1 using the following regimen: 3 mU/m^2 on Day 1; 5 mU/m^2 on Day 2; 10 mU/m^2 on Day 3; and 20 mU/m^2 on Days 4–10. Four additional patients received a very similar schedule (20 mU/m^2/day × 10 days) after being intolerant to 30 mU/m^2/day × 10 days. Fever, chills, myalgias, and malaise were universal. Twenty-seven percent of the patients experienced a decline in PS of two or more levels and 33% experienced weight loss $\geq 10\%$ during therapy. Mild leukopenia was noted in many patients: wbc count nadir between 1000 and 1999/mm^3 occurred in 36% of the patients and between 2000 and 2999/mm^3 occurred in 31%. One patient experienced a total wbc count < 1000/mm^3. Median day of wbc count nadir was Day 7. One patient had a platelet count $< 100{,}000$/mm^3. No infectious or bleeding complications related to therapy were noted. Reduced leukocyte counts recovered promptly with cessation or reduction of IFN-αn1; all counts had recovered by the time the next treatment was due.

SGOT increased to greater than four times baseline in 45% of the patients. In these patients the interferon dose was reduced by 50%. No significant change in SGOT subsequently occurred. No patient developed liver tenderness, enlargement, or icterus. Five patients developed a serum creatinine > 2 mg/dl during the first cycle of therapy. One of these patients died 14 days after beginning therapy with renal failure (serum creatinine, 10 mg/dl) and pneumonia (wbc count, normal). The extent to which interferon contributed to the renal impairment in this patient is uncertain. In each of the other four patients creatinine returned to baseline levels 21–28 days after beginning therapy.

The toxic effects were such that only 30% of the patients entered at the $3 \rightarrow 20$-mU/m^2 dose were able to complete two cycles of therapy without dose reduction or treatment interruption and only 18% of the patients received more than two cycles without dose reduction.

Response

Repeated cycles of treatment were possible with reduced doses. Among 39 evaluable patients, the median number of treatment cycles administered was three: 26 patients stopped therapy because of progressive disease having never obtained a response; and six discontinued therapy because of toxicity or intercurrent disease-related complications. Five patients (13%) achieved partial response. At the time of this analysis, two patients have continued therapy for 16 and 17 months with stable disease having never achieved a response. Among the five patients who had partial response in measurable tumor, four had responses in measurable pulmonary metastases, while one had a response in a pelvic mass measurable by computerized tomographic scan. Four of these patients were entered initially in Schedule B; the fifth patient received 5 days of Schedule A and subsequently received five cycles of IFN α-n1 at a reduced dose ($3 \rightarrow 10$ mU/m^2). Median duration of therapy prior to response was 140 days (range, 49–169). Characteristics of patients with partial response are shown in table 2.

TABLE 2.—Characteristics of responding patients

Age (yrs)	Sex	Initial PS	Duration of disease*	Time to partial response (days)	Duration of response (mos)
25	Male	1	6–12 mos	74	6.8
56	Male	1	> 5 yrs	169	8.1+
62	Male	0	6–12 mos	140	2.8
65	Male	2	6–12 mos	147	11.4
62	Male	0	12 mos	48	14.6

*Interval from diagnosis of RCC to entry in trial.

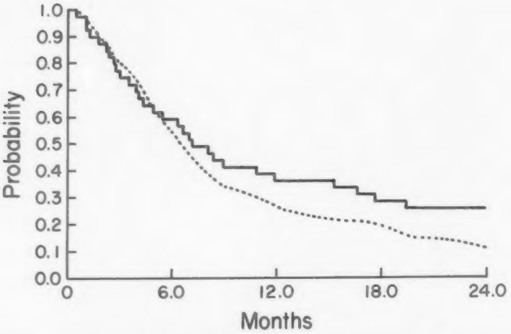

FIGURE 1.—Survival of 39 eligible patients treated with IFN α-n1 in this phase II pilot study (——) compared to the survival of 332 previously untreated patients with a PS of 0, 1, or 2 entered in several ECOG phase II trials in metastatic RCC (····).

Survival

Survival measured from date of registration is shown in figure 1 and is compared to the survival of 332 previously untreated patients with a PS of 0, 1, or 2 entered in ECOG phase II trials in RCC between 1974 and 1983. Drugs evaluated in these studies were: cyclophosphamide, megestrol, etoposide, and galactitol (EST-1874); Baker's antifol, dactinomycin, vinblastine, lomustine, PALA, and amsacrine (EST-3877); bisantrene and PCNU (EST-1880); and vinblastine and L-alanosine (EST-1882). Median survival of patients receiving IFN α-n1 is 7.1 months, which is indistinguishable from that noted for the group of 332 patients. It is of interest that eight patients (21%) who received IFN α-n1 are alive ≥ 2 years after beginning therapy. This is somewhat higher than the 2-year survival rates in prior ECOG phase II studies ranging from 2% to 14%. It is noteworthy that only two of these "long-term" survivors had had an objective response to IFN α-n1; the other six had either progressed on therapy or had had stable disease but unacceptable toxicity. It is tempting to suggest that a cohort of patients in this trial had prolonged survival because of IFN α-n1 therapy. However, the survival times of the interferon-treated patients and prior patients are only very roughly comparable due to the long period over which the patients in prior ECOG studies were treated. The authors believe that this analysis does not support the conclusion that interferon treatment improved survival.

Initial PS, time from initial diagnosis, prior nephrectomy, presence of weight loss prior to therapy, presence of lung metastases, age (< 60, 60-69, and ≥ 70 years), and sex were examined to determine whether these individual characteristics were prognostic for survival. Only the absence of weight loss prior to therapy was significantly related to improved survival ($P < 0.001$, log-rank test).

Pharmacokinetics of IFN α-n1

Plasma levels of interferon were measured by bioassay (Bioassay Systems Corporation, Woburn, MA) in 24 patients receiving the 3 → 20-mU/m^2 schedule (12). Blood samples were obtained before treatment on Days 4, 5, 7, 8, 10, and 11. Blood samples obtained 6 hours after IFN α-n1 administration were obtained on Days 4, 7, and 10. Median 6-hour plasma interferon titers were 500, 700, and 725 U/ml on Days 4, 7, and 10, respectively (fig 2). There was substantial variation in serum interferon activity (eg, range of peak concentrations at Day 10 was 600-1000 U/ml). Concentrations of interferon > 200 U/ml were achieved in all patients and appeared to be maintained for 5 days during administration of 20 mU/m^2/day.

DISCUSSION

Trials of cytotoxic therapy in patients with advanced RCC have been uniformly disappointing. No agent or combination of agents has been shown to result reproducibly in significant tumor regression in $> 20\%$ of the patients and no impact on survival has been demonstrated (1,13).

Alpha interferons produced from eukaryotic cells or by bacterial recombinant DNA technology have been evaluated in advanced RCC. Response rates between 10% and 31% have been reported (2-8). No type of interferon, dose, or schedule has been shown to be superior to any other.

Quesada et al (4) have reported a randomized trial which suggests that recombinant interferon alpha A (rIFN αA) is more effective at a dose of 20 mU/m^2/day than a dose of 2 mU. That study also suggests that the therapeutic efficacy of rIFN αA may be limited by the development of antibodies to this product (4). Kirkwood et al (8) also found that higher doses of α-interferon (10 mU/day × 28 days) may be superior to lower doses (1 mU/day × 28 days). Neither of these studies included an adequate number of patients to draw conclusions regarding dose-response relationships. Tuttle et al (14) have evaluated 267 patients treated with IFN α-nl (including the 40 reported here) in six phase II trials. Doses administered ranged from 3 to 50 mU on various schedules. An overall response rate of 14% was noted. No dose or schedule showed superiority in this cross-study analysis and no individual patient response predictors were identified. No patients with RCC have been found to have neutralizing substances (ie, antibodies) to IFN α-n1,[11] and no patients receiving IFN α-n1 have developed amelioration of the immediate systemic symptoms of IFN injection as has been noted to occur with other interferons when antibodies were detected (4).

It has been suggested that prolonged interferon therapy is necessary to see responses in RCC (2). Intervals

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[11] Tuttle R. Unpublished observation. Data on file. Burroughs Wellcome Co, Dec 1985.

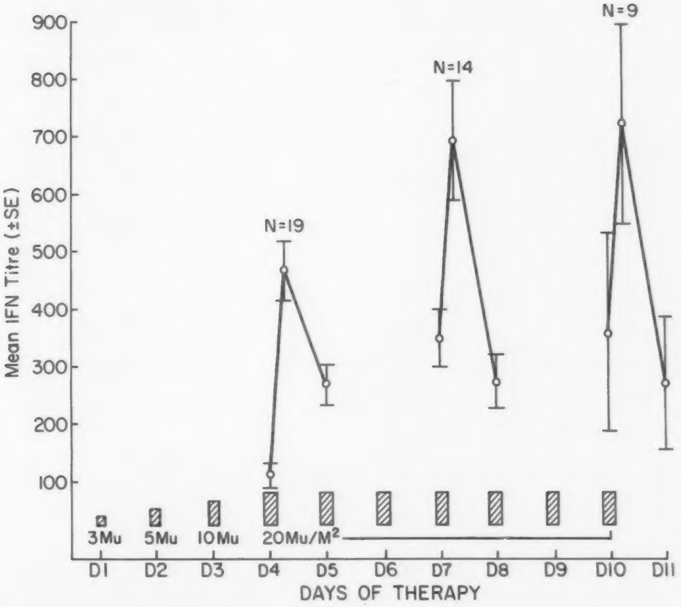

FIGURE 2.—Serum interferon activity (bioassay) in 24 patients during induction cycles of HL-IFN therapy. Data on Days 4, 7, and 10 are values from predose, 6 hrs postdose, and immediately prior to the next day's dose of IFN α-n1.

from initiation of treatment to documentation of response have been 4-6 months; it is noteworthy that four of five responses in our study occurred after ≥ 2½ months of therapy. It is possible that a more tolerable dose and schedule which would permit more prolonged therapy would result in an improved response. This has not been observed in other trials, however.

The role of α-interferons in advanced RCC is limited. However, objective responses to interferons appear to occur more frequently than with other available systemic treatments. Approaches currently being evaluated which may demonstrate enhanced utility include combinations of IFN α with cytotoxic drugs (15), IFN β, IFN γ, and combinations of interferons. Trials of interferon as a surgical adjuvant for patients at high risk of recurrence after radical nephrectomy also are being considered. At this time, IFN α offers limited benefit for patients with metastatic RCC.

REFERENCES

1. Hrushesky WJ, and Murphy GP. Current status of the therapy of advanced renal carcinoma. J Surg Oncol 9:277-288, 1977.
2. Quesada JR, Swanson DA, Trindade A, et al. Renal cell carcinoma: antitumor effects of leukocyte interferon. Cancer Res 43: 940-947, 1983.
3. Quesada JR, Swanson DA, and Gutterman JU. Phase II study of alpha interferon in metastatic renal cell carcinoma. A progress report. J Clin Oncol 3:1086-1092, 1985.
4. Quesada JR, Rios A, Swanson D, et al. Antitumor activity of recombinant-derived interferon alpha in metastatic renal cell carcinoma. J Clin Oncol 3:1, 1985.
5. Magnusson K, Christophersen IS, Jordal R, et al. Interferon therapy in recurrent renal carcinoma. Acta Med Scand 213: 221-223, 1983.
6. Dekernion JB, Sarna G, and Figlin R. The treatment of renal cell carcinoma with human leukocyte alpha interferon. J Urol 130:1063-1066, 1983.
7. Neidhart JA, Gagen MM, Young D, et al. Interferon-α therapy of renal cancer. Cancer Res 44:4140-4143, 1984.
8. Kirkwood JM, Harris JE, Vera R, et al. Randomized trial of low and high doses of leukocyte interferon in metastatic renal cell carcinoma. Cancer Res 45:863-871, 1985.
9. Rohatiner AZS, Balkwill FR, Griffin DB, et al. A phase I study of human lymphoblastoid interferon administered by continuous intravenous infusion. Cancer Chemother Pharmacol 9:97-102, 1982.
10. Finter NB, and Fantes KH. The purity and safety of interferon prepared for clinical use: the case of lymphoblastoid interferon. *In* Interferon (Gresser L, ed). London, Academic Press, Inc, 1980, vol 2, pp 65-80.
11. Oken MM, Creech R, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.
12. Armstrong J. Semimicro dye binding assay for rabbit interferon. Applied Microbiol 21:723-725, 1982.
13. Torti FM. Treatment of metastatic renal cell carcinoma. Recent Results Cancer Res 33:123-142, 1985.
14. Tuttle R, Wold D, Neidhart J, et al. (Abstr 1) Analysis of human lymphoblastoid interferon, Wellcome (Wellferon®) in the treatment of advanced renal cell carcinoma (ARCC). Antiviral Res 3:95, 1984.
15. Aapro M, Alberts DS, and Salmon SE. Interactions of human leukocyte interferon with vinca alkaloids and other chemotherapeutic agents against human tumors in clonogenic assay. Cancer Chemother Pharmacol 10:161-166, 1983.

Phase II Trial of Carboplatin in Advanced Malignant Melanoma[1,2]

Lydia M. Evans,[3] Ephraim S. Casper,[3,*] Richard Rosenbluth,[4] and Participating Community Clinical Oncology Program Investigators[5]

Twenty-six evaluable patients with metastatic malignant melanoma who had not received prior chemotherapy were treated in a phase II study with carboplatin (CBDCA), 400 mg/m^2 iv every 4 weeks. There were five partial responses of 3, 3+, 5, 7+, and 12+ months' duration. Thrombocytopenia was the dose-limiting toxicity; ten patients had transient platelet count depressions to $< 75{,}000$/mm^3. Mild to moderate nausea and/or vomiting occurred in 15 patients. Renal, auditory, and neurologic toxic effects were not encountered. Since the response rate of 19% (95% confidence limits, 8%–38%) is similar to that noted for dacarbazine, carboplatin, singly and in combination with other agents, needs further evaluation in patients with malignant melanoma. [Cancer Treat Rep 71:171-172, 1987]

Cisplatin, both alone and in combination, has been evaluated in the treatment of patients with metastatic malignant melanoma, with response rates in the range of 10%–25% (1-6). Carboplatin (CBDCA) is a second-generation platinum analog with a spectrum of toxicity different from cisplatin while retaining antitumor activity in animal models (7). In two phase I clinical trials, therapeutic responses were noted in patients with advanced malignant melanoma (8,9). The dose-limiting toxicity was myelosuppression, with thrombocytopenia being more common than leukopenia. Nausea and vomiting were generally less severe and of shorter duration than that seen with cisplatin, while nephrotoxicity, ototoxicity, and neurotoxicity were uncommon. We report the results of a phase II trial of CBDCA in patients with advanced malignant melanoma who had not received prior chemotherapy.

PATIENTS AND METHODS

Eligibility criteria for this protocol required that patients have measurable disease, no prior chemotherapy, a Karnofsky performance status of at least 60%, no radiation therapy or immunotherapy for the preceding 4 weeks, wbc count > 4000/mm^3, platelet count $> 150{,}000$/mm^3, creatinine < 1.5 mg/dl, total serum bilirubin < 1.5 mg/dl, and a life expectancy of at least 8 weeks.

CBDCA was supplied by the National Cancer Institute (NCI) (Bethesda, MD). The drug was administered as an iv infusion of 400 mg/m^2 over 1 hour, preceded and followed by 500 ml of 5% dextrose in one-half normal saline. The drug was given every 4 weeks, depending on hematologic recovery. A cbc and serum creatinine were obtained on Days 1 and 14 of each cycle, while a biochemical profile, physical examination with tumor measurements, and assessment of toxicity were done on the first day of each cycle. If nadir blood counts remained above entry level criteria, and other toxicity was acceptable, the next dose was escalated by 50 mg/m^2. If after a given dose the wbc count fell below 2000 cells/mm^3, the platelet count fell below 75,000/mm^3, or other unacceptable toxic effects were encountered, the next dose was reduced by 50%. Standard response criteria were used.

RESULTS

A total of 30 patients entered the trial, 16 from Memorial Sloan-Kettering Cancer Center and 14 from participating Community Clinical Oncology Program (CCOP) investigators. Twenty-seven were eligible for the study (two had received prior chemotherapy and one had an inadequate platelet count). All but one of the eligible patients (a 66-year-old woman with brain metastases who died 20 days after her first dose of chemotherapy) were evaluable for therapeutic response. The

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[4] Hackensack Medical Center, NJ.

[5] We thank Karen Sheehan and Phyllis Hollander for assistance with data collection.

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TABLE 1.—Characteristics of evaluable patients

Characteristic	No. of patients
Males/females	9/17
Median age in yrs (range): 56 (27–75)	
Karnofsky status	
90	8
80	9
70	5
60	4
Prior radiation therapy	4
Prior immunotherapy	3
Dominant site of measurable disease	
Nodes/soft tissue/skin	8
Lung	7
Liver/intra-abdominal	11

characteristics of the evaluable patients are shown in table 1. The median number of doses of CBDCA was two (range, one to 12), with the median total dose being 850 mg/m^2 (range, 400–5690).

Five patients achieved partial responses lasting 3, 3+, 5, 7+, and 12+ months. Sites of disease regression in patients included skin (one), liver (one), lung (two), peripheral lymph nodes (two), and retroperitoneal lymph nodes (two). All responses were associated with improvement in symptoms. The two patients whose responses have ended developed CNS metastases while on therapy. However, CBDCA continued to control peripheral disease for an additional 5 months in one and 2+ months in the other. Stable disease was noted in six patients for periods of 3–6 months. There were no complete responses.

Two of the 26 eligible patients were not evaluable for hematologic toxicity because they failed to obtain interim blood tests. In the 24 remaining patients, the dose-limiting toxicity was thrombocytopenia. The median nadir platelet count was 97,000/mm^3 (range, 27,000–450,000), occurring at Day 15 (range, Day 8–34). Ten patients had transient platelet count depressions below 75,000/mm^3. The median nadir wbc count was 4100/mm^3 (range, 2300–21,000), which occurred at Day 22 (range, Day 8–41). The dose was escalated in seven patients; however, there appeared to be cumulative myelotoxicity, and the dose was eventually reduced in four patients. Fifteen patients experienced mild to moderate nausea and/or vomiting. A disease-related rise in serum creatinine from 1.1 mg/dl to 1.6 mg/dl was seen preterminally in one patient, another experienced minimal alopecia, and two complained of mild generalized malaise. Clinically, there was no ototoxicity or neurotoxicity.

DISCUSSION

The treatment of advanced malignant melanoma remains a difficult therapeutic problem. The demonstrated therapeutic activity of cisplatin, alone and in combination, provided a stimulus for our trial with CBDCA. CBDCA appears to have comparable activity to the parent compound (19%; 95% confidence limits, 8%–38%), with substantially less toxicity when used as a single agent in this disease. It can be easily administered in the outpatient setting, as demonstrated by the active participation of CCOP investigators in this trial. The recent preliminary reports of high response rates for cisplatin in combination with DTIC (10) and for cisplatin with WR-2721 (11) are encouraging. Since neither DTIC nor WR-2721 appears to cause major hematologic toxicity, serious consideration should be given to trials combining CBDCA with one or both of these agents. In addition, CBDCA should be evaluated as salvage chemotherapy for patients with advanced melanoma resistant to other chemotherapeutic agents.

REFERENCES

1. AL-SARRAF M, FLETCHER W, OISHI N, ET AL. Cisplatin hydration with and without mannitol diuresis in refractory disseminated malignant melanoma: a Southwest Oncology Group study. Cancer Treat Rep 66:31–35, 1982.
2. KARAKOUSIS CP, GETEZ EP, BJORNSSON S, ET AL. *cis*-Dichlorodiammineplatinum(II) and DTIC in malignant melanoma. Cancer Treat Rep 63:2009–2010, 1979.
3. NATHANSON L, KAUFMAN SD, and CAREY RW. Vinblastine infusion, bleomycin and *cis*-dichlorodiammineplatinum(II) chemotherapy in metastatic melanoma. Cancer 48:1290–1298, 1984.
4. CREAGAN ET, AHMANN DL, SCHUTT AJ, ET AL. Phase II study of the combination of vinblastine, bleomycin and cisplatin in advanced malignant melanoma. Cancer Treat Rep 66:567–569, 1982.
5. LUIKART SD, KENNEALEY GT, and KIRKWOOD JM. Randomized phase III trial of vinblastine, bleomycin and *cis*-dichlorodiammineplatinum(II) versus dacarbazine in malignant melanoma. J Clin Oncol 2:164–168, 1984.
6. CAREY RW, ANDERSON JR, GREEN M, ET AL. Treatment of metastatic malignant melanoma with vinblastine, dacarbazine, and cisplatin: a report from the Cancer and Leukemia Group B. Cancer Treat Rep 70:329–331, 1986.
7. WOLPERT-DEFILIPES MK. Antitumor activity of cisplatin analogs. *In* Cisplatin—Current Status and New Developments (Prestayko AW, Crooke ST, and Carter SK, eds). New York, Academic Press, Inc, 1980, pp 183–191.
8. KELSEN D, and BAJORIN D. Phase I trial of carboplatin (C), vindesine (V), and bleomycin in advanced solid tumors. Proc ASCO 5:156, 1986.
9. VAN ECHO DA, EGORIN MJ, WHITACRE MY, ET AL. Phase I clinical and pharmacologic trial of carboplatin daily for 5 days. Cancer Treat Rep 68:1103–1114, 1984.
10. FLETCHER J, DANA B, JEWELL W, ET AL. Evaluation of cisplatinum and DTIC combination chemotherapy in disseminated malignant melanoma: a SWOG phase II pilot study. Proc ASCO 5:510, 1986.
11. GLOVER D, GLICK J, WEILER C, ET AL. Phase II trial of WR-2721 and cis-platinum (DDP) in metastatic melanoma. Proc ASCO 5:558, 1986.

Survey of the Effect of Adding Fluosol-DA 20%/O_2 to Treatment With Various Chemotherapeutic Agents[1,2]

Beverly A. Teicher* and Sylvia A. Holden[3]

The tumor growth delays (TGDs) observed with a series of antineoplastic agents with or without Fluosol-DA and carbogen breathing (95% oxygen, 5% carbon dioxide) in the FSaIIC fibrosarcoma are shown. All but two of eleven alkylating agents examined showed some degree of positive effect by the addition of Fluosol-DA and carbogen breathing to drug treatment. The largest effects were seen with busulfan and procarbazine. Melphalan and the nitrosoureas, carmustine, lomustine, semustine, and chlorozotocin, gave increases in TGD ranging from 2- to 6-fold with the addition of Fluosol-DA and carbogen breathing. Modest increases were seen with cytoxan and dacarbazine. Cisplatin showed no additional TGD with Fluosol-DA and carbogen breathing, and mitomycin showed a negative effect. The addition of Fluosol-DA and carbogen breathing to bleomycin treatment increased the TGD produced by 5- to 6-fold compared to the drug alone. With vincristine and etoposide at three different doses, TGDs increased 2.4- to 3-fold in combination with Fluosol-DA and carbogen breathing. Increases of 1.3- to 1.4-fold in the TGD were observed with methotrexate and 5-fluorouracil with Fluosol-DA and carbogen breathing. Adding Fluosol-DA and carbogen breathing to treatment with several of the drugs examined resulted in significant enhancement of TGD and therefore may lead to an improved therapeutic outcome when added to certain currently used clinical regimens. [Cancer Treat Rep 71:173-177, 1987]

Hypoxia has long been known to protect cells from the cytotoxic effects of irradiation. The hypoxic cells in solid murine tumors limit the responses of these neoplasms to treatment with ionizing irradiation delivered as a single fraction, and the hypoxic cells surviving large doses of irradiation are capable of either reestablishing the tumor in situ or producing tumors in other animals upon transplantation (3,8,28).

The level of cellular oxygenation is also an important factor in the action of many antineoplastic agents, several of which have been classified by their selective toxic effects toward oxygenated and hypoxic tumor cells (26). Reactive free radicals of oxygen may be responsible for the cleavage of DNA by several agents including bleomycin, procarbazine, streptonigrin, dactinomycin, and doxorubicin. Cells which are hypoxic may be either noncycling or slowly progressing through the cell cycle (3,8). Therefore, the cellular state of oxygenation may also have a strong influence on the cytotoxicity of antimetabolites, such as 5-fluorouracil and methotrexate, and vinca alkaloids such as vincristine, which are most lethal to cells that are progressing through the cell cycle.

Compounds which mimic the effect of oxygen in cells such as the radiosensitizer misonidazole have been shown to enhance the cytotoxicity of several antitumor alkylating agents including melphalan, cyclophosphamide, carmustine (BCNU), and lomustine (CCNU) in vitro and in vivo. This phenomenon has been termed chemosensitization or chemopotentiation (3). The potentiation of the antitumor effect of these drugs by misonidazole in vivo was seen without a similar increase in normal tissue toxicity. The presence of hypoxic cells in solid tumors may account for the preferential effect, since chemosensitization in vitro occurs only when cells are exposed to misonidazole under hypoxic conditions, ie, conditions in which reduction of misonidazole through formation of oxygen-mimicking free radicals can occur.

Perfluorochemicals have excellent oxygen-carrying and carbon dioxide-carrying capacity (5). To fully utilize the oxygen-carrying capacity of these materials, high partial pressures of oxygen are used. Unlike hemoglobin, where oxygen is bound to the molecule, the solvent action of the perfluorochemicals for oxygen does not involve any kind of chemical or chelating processes. The gas molecules situate themselves in the spaces be-

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tween the molecules (4,6). The uptake and release of oxygen from perfluorochemical emulsions are completely reversible. At least 90% of the emulsion particles in the preparation which we used are < 0.2 μm in diameter, much smaller than rbcs (average diameter, 5-10 μm).

The perfluorochemical emulsion Fluosol-DA, in combination with breathing a 100% or 95% oxygen atmosphere, has been shown to enhance the response of several solid rodent tumors to single dose and fractionated radiation treatment (16,29-31,36) with little influence on normal tissues (11,18). As a result of these studies, Fluosol-DA plus oxygen breathing has recently entered clinical trials in combination with radiotherapy in advanced head and neck cancer (20).

In this study, representative chemotherapeutic agents from several classes were tested in a tumor growth delay (TGD) assay in combination with Fluosol-DA under conditions of normal aeration or with carbogen breathing to determine whether the antitumor activity of these drugs would be improved.

MATERIALS AND METHODS

Materials

Fluosol-DA 20% (Green Cross Corp, Osaka, Japan) was obtained from Alpha Therapeutics Corp (Los Angeles, CA). The stem emulsion consists of 25% (wt/vol) perfluorochemicals: seven parts perfluorodecalin; three parts perfluorotripropylamine; Pluronic F-68 (2.7%, wt/vol); yolk phospholipids (0.4%, wt/vol) as emulsifiers; and glycerol (0.8%, wt/vol) as a cryoprotecting agent. The annex solution (electrolyte/bicarbonate solution) furnishes the preparation with physiological osmolarity. The stem emulsion particles are 1.82×10^8 cm^2/L available for oxygen diffusion (about 100 times the surface area of the rbc in whole blood). The half-life of Fluosol-DA in vivo is about 12 hours in rodents (5).

BCNU, CCNU, cyclophosphamide (Cytoxan), mitomycin (Mutamycin), procarbazine (Matulane), dacarbazine (DTIC), vincristine (Oncovin), methotrexate (Mexate), and 5-fluorouracil (fluorouracil) were obtained from the Dana-Farber Cancer Institute pharmacy. Semustine (MeCCNU) and chlorozotocin were gifts from Mr. L. Kedda, Drug Synthesis and Chemistry Branch, National Cancer Institute. Cisplatin (CDDP) was a gift from Dr. Michael Abrams, Johnson Matthey Inc, West Chester, PA. Bleomycin (Blenoxane) and etoposide (VP-16) were provided by Bristol Laboratories Inc, Syracuse, NY. Melphalan (L-phenylalanine mustard) was a gift from Burroughs Wellcome Co, Research Triangle Park, NC. Busulfan was purchased from Sigma Chemical Co, St. Louis, MO.

Tumors

The FSaII fibrosarcoma (15) adapted for growth in culture (FSaIIC) (29) was carried in C3H/Be/FeJ male mice (Jackson Laboratory, Bar Harbor, ME).

Tumor Growth Delay Experiments

For experiments, 2×10^6 FSaII fibrosarcoma tumor cells were implanted sc in the flank of the mice. When the tumors were approximately 50 mm^3 in volume, the perfluorochemical emulsion Fluosol-DA (0.3 ml) was injected via the tail vein. Immediately afterward the drug was administered by ip injection. The drugs were prepared in sterile phosphate-buffered 0.9% saline or as recommended for clinical administration. The animals were then allowed to breathe air or were placed in a circulating atmosphere of 95% O_2 and 5% CO_2 (carbogen) for 1 hour and then removed to air. The progress of each tumor was measured thrice weekly until it reached a volume of 500 mm^3. Measurements were made in three dimensions using calipers, and tumor volumes were calculated based on a hemiellipsoid. All of the measurements were made by the same investigator. TGD was calculated as the days taken by each individual tumor to reach 500 mm^3 compared to the untreated controls. Each treatment group had seven animals and the experiment was repeated three times. Days of tumor growth delay are the mean ± standard error for the treatment group compared to the control. The control groups included groups receiving no treatment with air or carbogen breathing and groups receiving Fluosol-DA with air or carbogen breathing. All of these control groups had identical tumor growth patterns (23,25,29, 30). Control FsaII tumors reach 500 mm^3 in 12.0 ± 0.2 days. The growth of control tumors from 55 mm^3 to 500 mm^3 is log-linear with time.

Data Analysis

Statistical comparisons were made using the Student t test. Data from the TGD experiments were analyzed using a computer program written in Basic for the Apple II+ microcomputer. The program first derives the best-fit curve for each individual set of tumor volume data and then calculates the median, mean, and SEM for each experimental group. The day on which each tumor reaches 500 mm^3 and the median, mean, and SEM are then derived. A second program provides statistical comparisons between any number of groups using the t test and deriving degrees of freedom and P values.

RESULTS

The TGDs observed with a series of antineoplastic agents with or without Fluosol-DA and carbogen breathing (95% oxygen, 5% carbon dioxide) are shown in table 1. All of the drugs were examined in the FSaII fibrosarcoma (15,29), which is a solid mouse tumor characterized by reliable, even growth in animals and moderate sensitivity to many chemotherapeutic agents. The FSaII fibrosarcoma metastasizes very rarely, thus allowing for a relatively long period of observation of the growth of the primary tumor. Fluosol-DA was administered immediately prior to each drug injection. Carbogen breathing was maintained for 1 or 2 hours as indicated. Fluosol-DA

TABLE 1.—Effect of the addition of Fluosol-DA/O_2 on the TGD produced by various chemotherapeutic agents

Drug	Drug dose (mg/kg)	Treatment schedule	TGD, Days			
			Drug/air	Drug/O_2	Drug/Fluosol-DA/air	Drug/Fluosol-DA/O_2
Alkylating Agents						
Melphalan	10	Single dose	2.7 ± 0.3	4.0 ± 0.6	6.5 ± 1.2	9.5 ± 1.4*
CDDP	10	Single dose	8.0 ± 1.7	8.2 ± 1.6	5.0 ± 1.6	8.4 ± 2.0
Cytoxan	100	Days 7, 9, 11, 13, 15	7.98 ± 0.78	8.96 ± 1.64	6.35 ± 2.14	11.40 ± 3.57
Busulfan	10	Days 7, 9, 11, 13, 15	1.10 ± 0.53	2.87 ± 0.98	4.47 ± 0.51	9.26 ± 2.14*
Mitomycin	2	Days 7, 9, 11, 13, 15	9.03 ± 0.72	3.01 ± 0.93	0.87 ± 0.57	5.33 ± 1.71
BCNU	15	Days 7, 9, 11, 13, 15	13.38 ± 1.47	14.13 ± 1.61	18.48 ± 2.78	26.03 ± 2.54†
CCNU	100	Days 7, 9, 11, 13, 15	3.14 ± 0.42	5.38 ± 1.01	4.88 ± 1.02	12.53 ± 2.25*
MeCCNU	20	Days 7, 9, 11, 13, 15	1.84 ± 0.61	3.25 ± 0.43	5.57 ± 1.78	13.35 ± 2.27*
Chlorozotocin	15	Days 7, 9, 11, 13, 15	1.56 ± 0.32	1.38 ± 0.42	3.69 ± 0.64	8.34 ± 1.35*
Procarbazine	20	Single dose	0.73 ± 0.23	0.21 ± 0.19	2.66 ± 0.87	11.16 ± 2.40†
Dacarbazine	400	Single dose	4.14 ± 0.63	6.2 ± 1.5	3.8 ± 0.52	6.8 ± 1.00
Antibiotics and Alkaloids						
Bleomycin	10	Days 6, 10, 13, 16	2.27 ± 0.7	4.69 ± 1.02	5.51 ± 2.26	14.56 ± 2.97*
	15	Days 6, 10, 13, 16	3.66 ± 1.0	5.55 ± 1.5	5.86 ± 1.6	16.89 ± 2.94*
Vincristine	1.5	Single dose	1.86 ± 0.43	3.14 ± 0.86	2.79 ± 1.01	4.83 ± 1.22
VP-16	10	Days 7-12	1.84 ± 0.33	3.09 ± 0.85	3.07 ± 0.89	4.49 ± 1.22
	15	Days 7-12	4.89 ± 0.68	7.86 ± 0.97	3.11 ± 0.67	11.54 ± 2.14*
	20	Days 7-12	6.96 ± 1.0	9.48 ± 1.24	3.95 ± 1.10	21.70 ± 2.68†
Antimetabolites						
Methotrexate	0.8	Days 7-12	2.23 ± 0.89	1.43 ± 0.57	0.58 ± 0.53	2.90 ± 0.67
5-Fluorouracil	40	Days 7-10	7.61 ± 0.56	7.72 ± 0.72	9.32 ± 0.88	10.47 ± 1.06

*$P < 0.001$.
†$P < 0.0005$.

with air breathing or carbogen breathing produces no effect on tumor growth (29). There was no increase in gross toxicity of these drugs, as measured by weight loss, with the addition of Fluosol-DA and carbogen breathing.

Alkylating Agents

The alkylating agents are a heterogenous class of anticancer drugs having in common the capacity to bifunctionally alkylate DNA. All but two of the alkylating agents showed some degree of positive effect by the addition of Fluosol-DA and carbogen breathing to drug treatment. The largest effects were seen with busulfan and procarbazine where there were 9- and 11-fold increases in TGD, respectively. Melphalan and the nitrosoureas, BCNU, CCNU, MeCCNU, and chlorozotocin, gave increases in TGD ranging from 2- to 6-fold with the addition of Fluosol-DA and carbogen breathing. Modest increases in TGD 1.3- to 1.6-fold were seen with cytoxan and dacarbazine in combination with Fluosol-DA and carbogen breathing compared to the drug treatment in air. CDDP showed no additional TGD with Fluosol-DA and carbogen breathing, and mitomycin showed a negative effect, ie, a smaller TGD in combination with Fluosol-DA and carbogen breathing.

Fluosol-DA with air breathing produced a varied pattern of changes in TGD with the alkylating agents. The TGD produced by BCNU and CCNU were unaffected by the addition of Fluosol-DA and air breathing. CDDP, cytoxan, mitomycin, and dacarbazine showed diminished TGD in combination with Fluosol-DA and air breathing. The largest decrease in TGD was seen with mitomycin where most of the antitumor activity of this drug was negated by the addition of Fluosol-DA and air breathing. With melphalan, busulfan, MeCCNU, chlorozotocin, and procarbazine, TGD was increased 2- to 4-fold with Fluosol-DA and air breathing. These increases were much smaller than those seen when carbogen breathing was added to the treatment regimen.

Antibiotics and Alkaloids

Bleomycin produces fragmentation of DNA in a reaction which is strictly dependent upon the presence of ferrous ions and molecular oxygen (10,13,22). The addition of Fluosol-DA and carbogen breathing to bleomycin treatment increased the TGD produced by 5- to 6-fold compared to the drug alone (table 1). With vincristine and VP-16 at three different doses, TGDs increased 2.4- to 3-fold in combination with Fluosol-DA and carbogen breathing compared to the drugs and air breathing.

With all of these agents, carbogen breathing in addition to drug treatment without Fluosol-DA produced modest increases in TGD from 1.4- to 2-fold. In all cases, carbogen breathing with Fluosol-DA enhanced TGD.

Fluosol-DA with air breathing produced a leveling effect on VP-16 so that the effectiveness of the drug at 15 mg/kg and 20 mg/kg with Fluosol-DA and air breathing was less than the drug alone. The TGD produced by bleomycin, vincristine, and 10 mg/kg of VP-16 was increased slightly with Fluosol-DA and air breathing.

Antimetabolites

Two drugs were examined from the group of antimetabolites, methotrexate and 5-fluorouracil. As can be seen from table 1, Fluosol-DA and 1 hour of carbogen breathing produced small increases of 1.3- to 1.4-fold in the TGD produced by either drug. Carbogen breathing lessened the TGD produced by methotrexate and produced no change in the TGD produced by 5-fluorouracil. Fluosol-DA with air breathing also diminished the efficacy of methotrexate but produced a slight enhancement in 5-fluorouracil TGD.

DISCUSSION

Solid tumors can be refractory to cytotoxic agents for several reasons, including (*a*) the limited penetration of many drugs to poorly vascularized regions of the tumor, and (*b*) the physiological heterogeneity of the cellular populations of solid tumors with respect to oxygenation and proliferation (9,26). Fluosol-DA and carbogen breathing may produce changes in vivo at several levels which could lead to enhancement of TGD by anticancer drugs. The emulsion particles of Fluosol-DA provide a lipophilic environment which may sequester some drugs and either protect them from rapid inactivation by metabolism or binding in circulation and thus lead to enhanced TGD, or prevent delivery of cytotoxic amounts of the drug to the target cells and result in diminished TGD. These possibilities are well evidenced in the varied results seen with Fluosol-DA and air breathing. The addition of carbogen breathing to the Fluosol-DA plus alkylating agent treatments led to positive effects on TGD with all of the drugs examined except CDDP and mitomycin. Mitomycin is regarded as the prototype bioreductive alkylating agent and is the only drug in this study which has been shown by many investigators to be more toxic toward hypoxic cells (7,12,14,17,32). Unlike the lack of effect on CDDP TGD and the very small enhancement of cytoxan TGD, quite marked effects have been seen with misonidazole plus these drugs in both TGD studies and tumor cell survival studies (2,19,21). With both of these drugs, the overall effect of Fluosol-DA and carbogen breathing appears to be the result of a lessening of drug efficacy due to sequestration in perfluorochemical particles and some enhancement due to oxygen, producing overall very little or no effect. Therefore, the mechanism of Fluosol-DA interaction with chemotherapeutic agents may be more complex than that of misonidazole.

Some of the largest enhancements in TGD with Fluosol-DA and carbogen breathing were seen with bleomycin. One interpretation of these results is that bleomycin may penetrate to many regions of a tumor in concentrations adequate to be effective and that intratumoral oxygen levels may be the limiting factor in bleomycin efficacy under normal conditions. The oxygen boost provided by the addition of Fluosol-DA and carbogen breathing would allow the bleomycin present in the tumor to be cytotoxic. Oxygen has also been implicated in one of the possible mechanisms of action of VP-16 involving redox chemistry of the quinone moieties in these molecules (1,33–35). The increase in TGD seen with these drugs in combination with Fluosol-DA and carbogen breathing tends to support the notion that oxygen is one important factor in the antitumor activity of these agents.

One possibility which may result from adding oxygen to a tumor environment is that cells which have been quiescent may have increased metabolic activity. Since in these experiments carbogen breathing was maintained for a relatively short period of time (1 hr), it is unlikely that metabolic activation could occur extensively in the tumor. Therefore, the very small effects of Fluosol-DA and carbogen breathing seen with the antimetabolites, methotrexate and 5-fluorouracil, are not surprising.

An enhancement in therapeutic efficacy can be achieved only if the increase in TGD is greater than any concomitant increase in normal tissue damage. The results of adding Fluosol-DA and oxygen breathing to irradiation treatment have been reported for several normal tissues including partially committed (CFU-GM) or pluripotent (CFU-S) stem cells of the bone marrow (18), CFU-GM of the spleen (18), skin (18), intestinal epithelial cells (11) and spermatogenic stem cells (11). In all of these tissues, except for a slight enhancement in skin reaction, there was no significant alteration in irradiation response by administration of Fluosol-DA. The response of bone marrow as measured by the CFU-GM assay has been examined with melphalan (23), BCNU (25), CCNU (25), and VP-16 (24) in combination with Fluosol-DA and carbogen breathing. Bone marrow survival was found to be unchanged compared to drug treatment alone in all cases. The pulmonary toxicity of the combination of Fluosol-DA and carbogen breathing with bleomycin was examined morphologically and by pulmonary lavage (27). Acutely after the combined treatment, there was a marked increase in the cellularity of the lungs of animals which received the combined treatment (27).

The findings reported here indicate that adding Fluosol-DA and carbogen breathing to treatment with several drugs including melphalan, busulfan, the nitrosoureas, procarbazine, and VP-16 resulted in a significant enhancement of TGD in the FSaIIC fibrosarcoma. Therefore, the addition of Fluosol-DA and carbogen breathing may lead to an improved therapeutic efficacy with many currently used clinical regimens. Studies are under way examining the effects of extended carbogen breathing times (up to 6 hrs) with Fluosol-DA and drugs such as the antimetabolites, cytoxan, and CDDP with which only small effects were observed with 1 or 2 hours of carbogen breathing. The possible use of hyperbaric oxygen with Fluosol-DA and chemotherapeutic agents is also under investigation.

REFERENCES

1. BACHUR N, GORDON S, and GEE MV. A general mechanism for microsomal activation of quinone anticancer agents to free radicals. Cancer Res 38:1745, 1978.
2. CLEMENT JJ, GORMAN MS, WODINSKY I, ET AL. Enhancement of antitumor activity of alkylating agents by the radiation sensitizer misonidazole. Cancer Res 40:4165, 1980.
3. FOWLER JF. Chemical modifiers of radiosensitivity—theory and reality: a review. Int J Radiat Oncol Biol Phys 11:665, 1985.
4. GEYER R. Review of perfluorochemical-type blood substitutes. *In* Proceedings of the Tenth International Congress for Nutrition: Symposium on Perfluorochemical Artificial Blood. Kyoto, Elsevier Press, 1975, p 3.
5. GEYER RP. Substitutes for blood and its components. *In* Blood Substitutes and Plasma Expanders. New York, AR Liss, 1978, p 1.
6. GEYER RP. Oxygen transport in vivo by means of perfluorochemical preparations. N Engl J Med 307:304, 1982.
7. KENNEDY KA, ROCKWELL S, and SARTORELLI AC. Preferential activation of mitomycin C to cytotoxic metabolites by hypoxic tumor cells. Cancer Res 40:2356, 1980.
8. KENNEDY KA, TEICHER BA, ROCKWELL SC, ET AL. The hypoxic tumor cell: a target for selective cancer chemotherapy. Biochem Pharmacol 29:1, 1980.
9. KENNEDY KA, TEICHER BA, ROCKWELL SC, ET AL. Chemotherapeutic approaches to cell populations of tumors. *In* Molecular Actions and Targets for Cancer Chemotherapeutic Agents. New York, Academic Press, p 85.
10. LOWN JW, and KIM S-K. The mechanism of bleomycin-induced cleavage of DNA. Biochem Biophys Res Commun 77:1150, 1977.
11. MASON KA, WITHERS HR, and STECKEL RJ. Acute effects of a perfluorochemical oxygen carrier on normal tissue of the mouse. Radiat Res 104:387, 1984.
12. MARSHALL RS, and RAUTH AM. Modification of the cytotoxic activity of mitomycin C by oxygen and ascorbic acid in Chinese hamster ovary cells and repair-deficient mutant. Cancer Res 46: 2709, 1986.
13. OBERLEY LW, and BUETTNER GR. The production of hydroxy radical by bleomycin and iron(III). FEBS Lett 97:47, 1979.
14. RAUTH AM, MOHINDRA JK, and TANNOCK IF. Activity of mitomycin C for aerobic and hypoxic cells in vitro and in vivo. Cancer Res 43:4154, 1983.
15. RICE L, URANO M, and SUIT HD. The radiosensitivity of a murine fibrosarcoma as measured by three cell survival assays. Br J Cancer 41:240, 1980.
16. ROCKWELL S. Use of perfluorochemical emulsion to improve oxygenation in a solid tumor. Int J Radiat Oncol Biol Phys 11:97, 1985.
17. ROCKWELL S, KENNEDY KA, and SARTORELLI AC. Mitomycin C as a prototype bioreductive alkylating agent: in vitro studies of metabolism and cytotoxicity. Int J Radiat Oncol Biol Phys 8:753, 1982.
18. ROCKWELL S, MATE TP, IRVIN CG, ET AL. Reactions of tumors and normal tissues in mice to irradiation in the presence and absence of a perfluorochemical emulsion. Int J Radiat Oncol Biol Phys 12:1315–1318, 1986.
19. ROSE CM, MILLAR JL, PEACOCK JH, ET AL. Differential enhancement of melphalan cytotoxicity in tumors and normal tissue by misonidazole. *In* Radiation Sensitizers: Their Use in the Clinical Management of Cancer. New York, Masson, 1980, p 250.
20. ROSE C, LUSTIG R, MCINTOSH N, ET AL. A clinical trial of Fluosol-DA in advanced head and neck cancer. Int J Radiat Oncol Biol Phys 12:1325, 1986.
21. STEPHENS TC, COURTENAY VD, MILLS J, ET AL. Enhanced cell killing in Lewis lung carcinoma and a human pancreatic-carcinoma xenograft by the combination of cytotoxic drugs and misonidazole. Br J Cancer 43:451, 1981.
22. SUGIURA Y. Production of free radicals from phenol and tocopherol by bleomycin-iron(II) complex. Biochem Biophys Res Commun 87: 649, 1979.
23. TEICHER BA, HOLDEN SA, and ROSE CM. Therapeutic enhancement of melphalan by an oxygen-carrying perfluorochemical emulsion. Int J Cancer 36:585, 1985.
24. TEICHER BA, HOLDEN SA, and ROSE CM. Effect of oxygen on the cytotoxicity and antitumor activity of etoposide. JNCI 75:1129, 1985.
25. TEICHER BA, HOLDEN SA, and ROSE CM. Effect of Fluosol-DA/O_2 on tumor cell and bone marrow cytotoxicity of nitrosoureas in mice bearing FSaII fibrosarcoma. Int J Cancer 38:285, 1986.
26. TEICHER BA, LAZO JS, and SARTORELLI AC. Classification of antineoplastic agents by their selective toxicities toward oxygenated and hypoxic tumor cells. Cancer Res 41:73, 1981.
27. TEICHER BA, LAZO JS, MERRILL WW, ET AL. Effect of Fluosol-DA/O_2 on the antitumor activity and pulmonary toxicity of bleomycin. Cancer Chemother Pharmacol, 1986. In press.
28. TEICHER BA, and SARTORELLI AC. Selective attachment of hypoxic tumor cells. *In* Design of Models for Screening of Therapeutic Agents for Cancer. New York, Van Nostrand Reinhold, 1981, p 19.
29. TEICHER BA, and ROSE CM. Perfluorochemical emulsion can increase tumor radiosensitivity. Science 223:934, 1984.
30. TEICHER BA, and ROSE CM. Sensitization of solid mouse tumor to x-ray treatment by oxygen-carrying perfluorochemical emulsion. Cancer Res 44:4285, 1984.
31. TEICHER BA, and ROSE CM. Effect of dose and scheduling on growth delay of the Lewis lung carcinoma produced by the perfluorochemical emulsion, Fluosol-DA. Int J Radiat Oncol Biol Phys 12:1311, 1986.
32. TOMASZ M, and LIPMAN R. Reductive metabolism and alkylating activity of mitomycin C induced by rat liver microsomes. Biochemistry 20:5056, 1981.
33. VAN MAANEN JM, HOLTHUIS JJ, GOBAS F, ET AL. Role of bioactivation in covalent binding of VP-16 to rat liver and HeLa cell microsomal proteins. Proc Am Assoc Cancer Res 24:319, 1983.
34. WOZNIAK AJ, and ROSS WE. DNA damage as a basis for 4′-demethylepipodophyllotoxin-9-(4,6-*O*-ethylidene-α-D-glucopyranoside) (etoposide) cytotoxicity. Cancer Res 43:120, 1983.
35. WOZNIAK AJ, GLISSON BS, HANDE KR, ET AL. Inhibition of etoposide-induced DNA damage and cytotoxicity in L1210 cells by dehydrogenase inhibitors and other agents. Cancer Res 44:626, 1984.
36. ZHANG WL, PENCE D, PATTEN M, ET AL. Enhancement of tumor response to radiation by Fluosol-DA. Int J Radiat Oncol Biol Phys 10:172, 1984.

BRIEF REPORTS

Gonadal and Sexual Function in Male Patients With Hairy Cell Leukemia: Lack of Adverse Effects of Recombinant α2-Interferon Treatment[1,2]

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Gonadal and sexual function was evaluated in 81 male patients with hairy cell leukemia (HCL). Forty-eight patients were receiving recombinant α2b-interferon (INF) therapy, and 33 patients were receiving no systemic therapy at the time of evaluation. Among 28 patients with stable HCL who were receiving no systemic therapy, elevated serum follicle-stimulating hormone (FSH) was observed in two patients, while serum luteinizing hormone (LH) was normal in all. Serum testosterone levels were below normal in seven of 28 patients on no systemic therapy. Hormone levels were followed prospectively for a median of 8 months in 11 patients receiving INF without prior chlorambucil therapy. FSH became elevated in only one of eight patients with normal pretreatment values, LH remained normal in all patients, and testosterone transiently fell in two of four patients with normal pretreatment values. In addition, 20 of 29 patients receiving INF who had normal FSH and LH levels when first examined continued to have normal levels during a median of 10 months of INF therapy. Patients receiving INF generally reported either no change or improvement in sexual function as therapy progressed. We conclude that most patients with stable HCL have normal testicular function and that INF therapy does not appear to produce significant gonadal toxicity. [Cancer Treat Rep 71:179-181, 1987]

Hairy cell leukemia (HCL) is a chronic lymphoproliferative disorder characterized by an indolent clinical course compatible with a long survival (1). Splenectomy is frequently the initial treatment employed, although nearly one-half of splenectomized patients eventually relapse and require additional therapy (2). Though chlorambucil has been used with some success, recent studies have demonstrated that α-interferon can induce remission of HCL in most patients (3). At the University of Chicago, a phase II trial of α2b-interferon (INF) has been ongoing since October 1983. During this trial, a number of patients complained of problems with sexual function, and this prompted us to undertake an evaluation of sexual and gonadal function in patients with HCL. Our preliminary analysis of these data revealed that sexual dysfunction seemed to occur commonly in these patients (4). Preliminary endocrine evaluation demonstrated low serum testosterone levels in many patients, as well as elevated follicle-stimulating hormone (FSH) levels in 25%-30% of patients receiving INF therapy, suggesting a direct toxic effect of INF to the testicular germinal epithelium. Further follow-up of our HCL patient population, however, and prospective analysis of testicular function in a larger number of patients receiving INF fail to confirm our initial impressions that INF may produce significant gonadal toxicity.

PATIENTS AND METHODS

Eighty-one patients with a confirmed diagnosis of HCL are the subjects of this report. At the time of evaluation, 48 patients were receiving INF treatment; 19 of them had previously been treated with chlorambucil. Twenty-eight patients had stable disease requiring no systemic therapy (18 postsplenectomy), and five patients had previously received chlorambucil but were receiving no systemic therapy at the time of evaluation. Patients treated with INF all received α2b-interferon provided by the Schering Corporation (Kenilworth, NJ). The drug was administered by sc injection three times weekly at a dose of 2×10^6 units/m^2.

Patients at various points in their treatment were questioned about sexual desire, arousal, frequency of sexual contact, and frequency of orgasm. In addition, blood was obtained for determination of serum FSH, luteinizing hormone (LH), and testosterone. Radioim-

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munoassays for FSH and LH were performed in the Medicine Endocrinology Laboratory using a commercially available radioimmunoassay kit (Diagnostic Products, Los Angeles, CA), and testosterone determinations were done in the Pediatric Endocrinology Laboratory as previously described (5).

RESULTS

During the course of this study, serum FSH, LH, and testosterone levels were determined in 81 patients with HCL. In an attempt to gain some insight into the possible effects of HCL on testicular function, hormone levels were measured in 28 patients with stable disease who were receiving no systemic therapy. Among these 28 patients, serum FSH was elevated (> 20 mIU/ml) in two (7%), LH was normal (≤ 25 mIU/ml) in all, and testosterone was low (< 312 ng/dl) in seven (25%).

The effects of treatment for HCL on gonadal function were next examined. Of 24 patients who had previously received chlorambucil, 22 (92%) had elevated serum FSH levels consistent with the known toxic effect of chlorambucil to the germinal epithelium of the testis (6). Nine of these 24 patients (38%) also had elevated serum LH levels consistent with Leydig cell dysfunction. Eleven of the 24 patients (46%) had low serum testosterone levels.

Among the 29 patients receiving INF (median cumulative dose, 520×10^6 units; range, $108\text{-}972 \times 10^6$) without prior chlorambucil, nine (31%) had elevated serum FSH levels. Four of these nine individuals had had pretreatment FSH levels determined, and in three of the four, the values were above normal. Only two of the 29 patients receiving INF only had elevated serum LH levels, and one of these individuals had an abnormally elevated pretreatment level. Seventeen patients (59%) were also found to have subnormal testosterone levels during INF treatment. Pretreatment levels were available in 11 of these patients and were clearly below normal in seven prior to their beginning INF therapy. Thus, though many patients were found to have abnormal gonadotropin and/or testosterone levels during INF therapy, a number of these individuals also had abnormal hormone levels immediately prior to initiation of INF, raising the possibility that treatment actually had little effect on testicular function.

In an attempt then to better define the effects of INF therapy on gonadal function, we prospectively followed serum hormone levels in 11 patients who had no prior chlorambucil therapy and had serum hormone determinations at least once prior to the start of INF therapy. Serum FSH became elevated in only one of eight patients with normal pretreatment levels, LH remained normal in all eleven patients, and serum testosterone transiently fell in two of four patients with normal pretreatment values during a median of 8 months (range, 2–12) of INF therapy. Of seven patients with subnormal testosterone before treatment, three had a return to normal testosterone levels following initiation of INF therapy.

Also of note is that all 20 of the 29 patients receiving INF alone who had normal serum FSH and all 27 of the 29 patients who had normal serum LH levels when first examined continued to have normal hormone levels while receiving INF for a median of 10 months (range, 2–24) from the time of the initial gonadotropin determination. Thus, during the course of INF therapy, a rise in FSH from normal to elevated was observed in only one of 29 patients, while LH remained normal in all patients.

Clinical interviews were conducted in 76 of the 81 patients. Thirty-seven patients without prior chlorambucil therapy were interviewed prior to receiving interferon. Sexual dysfunction (decreased sexual desire, arousal, frequency of sexual contact, or frequency of orgasm) was reported by approximately 35% of these individuals. Of note is that patients interviewed just prior to initiation of INF therapy complained more frequently of sexual problems, particularly decreased desire (50% of patients) and frequency of contact (67% of patients), than patients not yet requiring INF therapy. While receiving INF, these individuals generally reported either no change or improvement in sexual desire and frequency as therapy progressed.

DISCUSSION

Our analysis of sexual and testicular function in patients with HCL demonstrates that most patients with stable HCL have normal gonadal function that is not significantly perturbed during the course of INF therapy. While a small number of patients have abnormally low serum testosterone levels prior to and during INF therapy, the physiological and clinical significance of this finding is uncertain, as low serum testosterone levels could not be correlated with elevated serum LH levels or with complaints of sexual dysfunction.

Interferon has recently been introduced as a new agent with significant activity in the treatment of HCL. Our data suggest that while testicular dysfunction may occasionally be observed in patients receiving INF therapy, it is not clearly related to a toxic effect of the drug. Indeed, in only one of 29 patients receiving INF alone could we unequivocally document a rise in serum FSH from normal before treatment to abnormal following initiation of INF therapy. All but two patients had persistently normal LH levels during the course of INF therapy.

HCL is a disease compatible with a long survival. Patient functional ability and quality of life thus become increasingly important in managing the illness and assessing the results of therapy. While we cannot exclude the possibility that INF causes gonadal toxicity in a small proportion of patients, our present findings fail to confirm our initial impressions that interferon might commonly cause testicular toxicity.

REFERENCES

1. GOLOMB HM, CATOVSKY D, and GOLDE DW. Hairy cell leukemia: a clinical review based on 71 cases. Ann Intern Med 89:677–683, 1978.
2. MINTZ U, and GOLOMB HM. Splenectomy as initial therapy in

twenty-six patients with leukemic reticuloendotheliosis (hairy cell leukemia). Cancer Res 39:2366-2370, 1979.

3. GOLOMB HM, RATAIN MJ, and VARDIMAN JW. Sequential treatment of hairy cell leukemia: a new role for interferon. *In* Important Advances in Oncology 1986 (DeVita VT, Hellman S, and Rosenberg SA, eds). Philadelphia, J.B. Lippincott Co, 1986, pp 311-321.
4. DAVIDSON HS, SCHILSKY RL, and GOLOMB HM. Gonadal and sexual function following treatment of hairy cell leukemia with recombinant alpha 2 interferon. Proc ASCO 4:232, 1985.
5. ISMAIL AA, NISWENDER GD, and MIDGLEY AR. Radioimmunoassay of testosterone without chromatography. J Clin Endocrinol 34: 177-182, 1972.
6. SCHILSKY RL, and SHERINS RJ. Gonadal dysfunction. *In* Cancer: Principles and Practice of Oncology, 2nd ed (DeVita VT, Hellman S, and Rosenberg SA, eds). Philadelphia, J.B. Lippincott Co, 1985, pp 2032-2039.

BRIEF REPORTS

High-Dose Carmustine With Autologous Bone Marrow Transplantation for the Adjuvant Treatment of High-Grade Gliomas of the Central Nervous System[1]

Steven N. Wolff,* Gordon L. Phillips, and Geoffrey P. Herzig[2]

The long-term survival of patients with high-grade gliomas of the CNS is poor despite the use of radiation therapy and chemotherapy. In an attempt to improve the survival of such patients, we administered adjuvant chemotherapy as high-dose carmustine with autologous bone marrow transplantation. Eighteen patients, 15 with glioblastoma multiforme and three with anaplastic astrocytoma, were treated shortly after completion of standard radiation therapy. One course of carmustine was administered at a total dose of 900-1050 mg/m^2 iv over 3 days followed in 3 days by the reinfusion of the previously cryopreserved bone marrow. Acute toxicity was mild, but eight patients had severe pulmonary or CNS toxicity of which four episodes of pulmonary toxicity were fatal. For all patients treated, the median survival was 17.5 months from diagnosis and the estimated probability of surviving $>$ 27 months was 22% (95% confidence limits of 14%-32%). Presently, there are four long-term survivors, two with progressive tumor, one suffering from severe encephalomyelopathy, and one alive and well. Although, in this series, we have observed long-term survivors, the overall estimated probability of survival is not substantially different from conventional treatment. In addition, the 22% incidence of fatal pulmonary toxicity suggests that this treatment will not measurably add to the treatment of CNS gliomas. **[Cancer Treat Rep 71:183-185, 1987]**

Current therapy of high-grade malignant gliomas of the CNS consists of debulking surgery followed by radiation therapy (1,2). Previous attempts to add chemotherapy as additional treatment have not substantially prolonged survival (3-5). Based on the preliminary data on recurrent tumors, we initiated a nonrandomized historically controlled study administering high-dose carmustine (BCNU) shortly after the completion of standard radiation therapy in patients with glioblastoma multiforme or anaplastic astrocytoma (6-9). We had hoped that this intense adjuvant treatment would both prolong survival and increase the proportion of long-term survivors. In this report we describe patient survival and toxicity.

MATERIALS AND METHODS

Patients.—Patients were treated at two institutions, Vanderbilt University and Washington University. Eligibility requirements were a histologic diagnosis of anaplastic astrocytoma or glioblastoma multiforme of the CNS, a good performance status (Eastern Cooperative Oncology Group 0 or 1), no severe visceral organ dysfunction not directly attributable to tumor, and a bone marrow biopsy without evidence of metastatic disease. Most patients were referred after the initial surgery and therefore no specific surgical procedure was required. Prior to bone marrow harvest and chemotherapy, appropriate informed consent was obtained.

Chemotherapy and radiation therapy.—Radiation was administered after surgery by the standard method of each institution. All patients received from 5000-6000 rads of brain irradiation. A single course of chemotherapy was given within 1-2 months after completion of radiation therapy and therefore by 3-4 months after diagnosis. BCNU was administered iv at a total dose of 900-1050 mg/m^2 given in equal aliquots over 3 consecutive days. Bone marrow was cryopreserved prior to the beginning of chemotherapy and reinfused 3 days after the completion of the chemotherapy.

Definitions and statistical methods.—Survival was determined from the day of pathological diagnosis. Estimation of the probability of survival was calculated by

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the method of Kaplan and Meier (10). The study was designed to detect a 2-year survival of > 40% based on the method of Makuch and Simon (11) and anticipated a total accrual of 16–38 patients. With the results of therapy of high-grade gliomas well established, the trial was to be compared to historical controls. Follow-up was through September 1986.

RESULTS

Patients.—A total of 18 patients were entered on this study with glioblastoma in 15 patients and anaplastic astrocytoma in three. Eleven patients were male and seven female. The median age of the patients was 33.5 years (range, 23–67). All patients had recovered from the effects of irradiation and were treated with BCNU at a median interval of 3 months after diagnosis (only one patient was delayed to > 4 months).

Survival.—Fourteen patients have died and four patients remain alive; two with progressive tumor at 25 and 42 months, one with severe encephalomyelopathy at 77 months, and one alive and well at 60 months. The estimated probability of survival beyond 27 months is 22% with 95% confidence limits of 14%–32%. All patients surviving free of disease had glioblastoma multiforme.

Complications.—Acute toxic effects of the therapy were mild and infrequent due to the delayed onset of myelosuppression which is characteristic of BCNU. However, late toxic effects were severe and frequent. Six patients developed BCNU lung toxicity with diffuse pulmonary infiltrates and hypoxemia within 1–4 months after BCNU of which four episodes were fatal. Two patients developed CNS deterioration not due to tumor and characterized as diffuse encephalomyelopathy that occurred up to 4 years after the BCNU.

DISCUSSION

Based on the theoretic value of high-dose therapy and the preliminary results obtained on treating patients with recurrent tumors, we administered high-dose BCNU with autologous bone marrow transplantation to patients with high-grade primary tumors of the CNS adjuvantly after the completion of radiation therapy. We used a nonrandomized study design since the historical data demonstrate consistently poor results. The study was designed to accrue between 16–38 patients to be able to detect a 2-year survival of 40% or better with an alpha-error of 0.05 and a beta-error of 0.20.

The maximal "safe" dose of BCNU with autologous bone marrow transplantation is 1200 mg/m^2 with a predicted fatal toxicity due to pulmonary complications of 10%–15% (12). The pulmonary toxicity of BCNU occurs also in standard dose with cumulative total doses of approximately 1200 mg/m^2 (13–15). To hopefully reduce this complication, we administered BCNU at a dose of 1050 mg/m^2.

With long-term follow-up of all of the patients, we have observed four long-term survivors with the estimated probability of surviving > 2 years at 22%. Two of the patients now have progressive tumor and two appear tumor free. Unfortunately, this magnitude of survival is not substantially improved compared to standard adjuvant treatment with BCNU. Ten patients have died due to tumor and four patients (22%) developed fatal pulmonary toxicity. Eliminating those patients who died due to drug toxicity from survival estimation does not appreciably alter the results, since tumor mortality occurred well after pulmonary toxicity.

The inherent toxicity of intense therapy is formidable. In essence, the patient is subjected to acute severe complications for the potential of long-term success. For many tumors treated with intense therapy, the acute mortality can be substantial. Yet, despite this extreme consequence, many patients with no expectation of survival with less intense approaches can achieve long-term success with intense therapy. Therefore, early toxicity must be weighed against the long-term benefits. However, in our series, the probability of survival is not substantially different from standard approaches to warrant this toxic treatment. Of note, is that when we further attempted to reduce pulmonary toxicity by decreasing the dose of BCNU to 900 mg/m^2, one of two patients treated at that dose died of pulmonary complications. The observed probability of fatal pulmonary toxicity observed in this series was higher than anticipated.

In summary, we attempted to improve the poor results of standard treatment of high-grade gliomas by augmenting the dose of BCNU. We were willing to accept a high complication rate if the end results were substantially improved compared to historical patient data. Unfortunately, the results of our series do not appear to be different from standard therapy. Although it could be argued that the observation of long-term survivors with high-grade gliomas is so rare that any success of this magnitude could be construed as beneficial, we do not believe that the high rate of morbidity would support this approach. Additionally, one of our long-term survivors had late-developing severe neurologic compromise probably due to the consequences of intense chemotherapy and radiation therapy (16,17). Although we have achieved some limited success, the results of this approach do not substantially change the overall bleak prognosis of patients with high-grade gliomas of the CNS.

REFERENCES

1. SHAPIRO WR. Therapy of adult malignant brain tumors. What have the clinical trials taught us? Semin Oncol 13:38–45, 1986.
2. WALKER MD, ALEXANDER E, JR, HUNT WE, ET AL. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas: a cooperative clinical trial. J Neurosurg 49:333–343, 1978.
3. BUTTI G, KNERICH B, and TANGHETTI B. Perioperative carmustine chemotherapy for malignant brain tumors. Cancer Treat Rep 68:1505–1506, 1984.
4. GREEN SB, BYAR DP, WALKER MD, ET AL. Comparisons of carmustine, procarbazine, and high-dose methylprednisolone as additions to surgery and radiotherapy for the treatment of malignant glioma. Cancer Treat Rep 67:121–132, 1983.
5. WALKER MD, GREEN SB, BYAR DP, ET AL. Randomized compari-

sons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. N Engl J Med 303:1323–1329, 1980.

6. PHILLIPS GL, WOLFF SN, FAY JW, ET AL. Intensive BCNU chemotherapy and autologous marrow transplantation for malignant gliomas. J Clin Oncol 4:639–645, 1986.
7. TAKVORIAN T, PARKER LM, HOCHBERG FH, ET AL. Autologous bone marrow transplantation: host effects of high-dose BCNU. J Clin Oncol 1:610–620, 1983.
8. HILDEBRAND J, BADJOU R, COLLARD-RONGE E, ET AL. Treatment of brain gliomas with high dose CCNU and autologous bone marrow transplantation. Biomedicine 32:71–75, 1980.
9. CARELLA AM, GIORDANO D, SANTINI G, ET AL. High-dose BCNU followed by autologous bone marrow infusion in glioblastoma multiforme. Tumori 67:473–475, 1981.
10. KAPLAN EL, and MEIER P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481, 1958.
11. MAKUCH RW, and SIMON R. Sample size considerations for non-randomized comparative studies. J Chron Dis 33:175–191, 1980.
12. PHILLIPS GL, FAY JW, HERZIG GP, ET AL. Intensive 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU), NSC-4366650 and cryopreserved bone marrow transplantation for refractory malignancies: a phase I-II study. Cancer 52:1792–1802, 1983.
13. MITSUDO SM, GREENWALD ES, BANERJI B, ET AL. BCNU lung. Drug induced pulmonary changes. Cancer 54:751–755, 1984.
14. ARONIN PA, MAHALEY MS, RUDNICK SA, ET AL. Prediction of BCNU pulmonary toxicity in patients with malignant glioma. N Engl J Med 303:183–188, 1980.
15. WEISS RB, POSTER DS, and PENTA JS. The nitrosoureas and pulmonary toxicity. Cancer Treat Rev 8:111–125, 1981.
16. SHELINE GE, WARA WM, and SMITH V. Therapeutic irradiation and brain injury. Int J Radiat Oncol Biol Phys 6:1215–1228, 1980.
17. BURGER PC, KAMENAR E, SCHOLD SC, JR, ET AL. Encephalomyelopathy following high-dose BCNU therapy. Cancer 48:1318–1327, 1981.

BRIEF REPORTS

Cytarabine, Cisplatin, and Etoposide Chemotherapy for Refractory Non-Hodgkin's Lymphoma[1,2]

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A phase II trial of cytarabine, cisplatin, and etoposide was conducted in 38 patients with refractory stage III and IV non-Hodgkin's lymphoma. There were two complete and nine partial responses (32%) among 35 evaluable patients. Response rate in patients with large cell lymphoma was 45%. The dose-limiting toxic effect was myelosuppression in 66% of patients. [Cancer Treat Rep 71:187–189, 1987]

Multiagent chemotherapy has produced impressive complete response rates in intermediate- and high-grade lymphomas (1,2). However, disease recurs in a significant number of patients after remission is attained; in addition, 20%–30% of patients are initially unresponsive to standard alkylator-anthracycline regimens. Survival in such situations is short. Cytarabine (Ara-C), cisplatin, and etoposide (VP-16) all have activity as single agents in lymphoid malignancy (3–5). Synergy has been reported with the combination of VP-16 and Ara-C in vitro and with teniposide and Ara-C in acute lymphoblastic leukemia (6). Cisplatin and VP-16 also appear to potentiate tumoricidal activity in clinical trials in other malignancies (7). These agents were combined in hopes of producing a non-cross-resistant "salvage" regimen for patients with refractory lymphoma.

PATIENTS AND METHODS

Thirty-eight patients with recurrent or refractory lymphoma, stage III or IV, were entered in the study. Patient characteristics are summarized in table 1. Initially the regimen consisted of Ara-C (300 mg/m^2 by continuous iv infusion × 24 hours on Day 1), cisplatin (80 mg/m^2 iv 12 hours after start of Ara-C on Day 1), and VP-16 (200 mg/m^2 iv over 1 hour following cisplatin on Day 1); Ara-C and VP-16 were given at the same doses on Day 8, with the Ara-C given by iv bolus. All patients received iv hydration for 12 hours before chemotherapy. Due to untoward toxicity in the initial ten patients, the Ara-C and VP-16 doses were decreased by 50% in the subsequent 28 patients. Therapy was repeated every 28 days for eight cycles in responding patients.

RESULTS

Three patients received only Day-1 chemotherapy at the initial dose and are not evaluable for response. All three patients were debilitated (performance status, 50%) and developed neutropenia, sepsis, and decreased renal function (serum creatinine between 3.0 and 7.0 mg/dl). One of these patients developed tumor lysis syndrome with metabolic acidosis and adult respiratory distress syndrome. Among the 35 evaluable patients, there were two complete responses and nine partial responses (32%). Among 11 patients with large cell lymphoma there were two complete and three partial responses (45%). Two of three patients with mycosis fungoides had partial responses, while only three of 13 patients with high-grade lymphoma had a response (table 1). Among 12 patients with marrow involvement, only one patient, who had a nodular poorly differentiated histology, had a response. Response did not correlate with drug dose administered; both complete re-

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TABLE 1.—Correlation of patient characteristics and response

Characteristics	No. of patients entered	No. of patients evaluable	No. of responses*	
			CR	PR
Sex				
Male	20	18	0	4
Female	18	17	2	5
Stage				
III	8	8	1	2
IV	30	27	1	7
Performance status (Karnofsky)				
50%-70%	18	15	0	5
80%-100%	20	20	2	4
Histologic grade				
Low	8	8	0	3
Intermediate	17	14	2	3
High	13	13	0	3
Marrow involvement	12	11	0	1
CNS involvement	3	3	0	0
Initial chemotherapy response				
Refractory	18	17	0	3
Response-relapse < 1 yr	10	9	1	4
Response-relapse > 1 yr	10	9	1	2
Prior therapy				
Radiation	14	11	0	3
1 chemotherapy combination	20	20	1	3
>1 chemotherapy combination	14	11	1	4

*CR = complete response; PR = partial response.

sponses and six of the nine partial responses occurred in patients receiving the low dose of Ara-C and VP-16. The proportion of patients with disease refractory to initial therapy was high in this study. There were fewer responses (three of 17 patients) in this group than in the group with some initial response (eight of 18); the difference, however, was not statistically significant. Performance status did not have any impact on response. The durations of the two complete responses were 22 and 28+ months, while partial responses were much shorter (3-7 months).

As was expected in heavily pretreated patients, hematologic toxicity was significant. Thirteen patients had wbc counts $< 2000/\mu l$ or platelet counts $< 50{,}000/\mu l$. Four of the ten patients at the initial Ara-C dose had wbc counts $< 1000/\mu l$; all these patients had clinical sepsis, two with early deaths. Following the dose modification, only one patient with marrow involvement had comparable cytopenia. Most patients with significant cytopenia (ten of 13) were in the poor-performance group; there was no correlation with marrow involvement. Half the patients required an additional 24-48 hours' hospitalization for gastrointestinal toxicity following Day-1 chemotherapy; reversible azotemia (creatinine > 2.0 mg/dl) occurred in one patient.

CONCLUSIONS

While chemotherapy with Ara-C, cisplatin, and VP-16 does show some activity in heavily pretreated patients with refractory lymphoma, the synergy expected from the in vitro data and by analogy from other clinical trials was disappointingly lacking. The VP-16 administration was scheduled midway in the Ara-C infusion because of preliminary reports of inhibition of Ara-C transport into tumor cells (8). More recent information suggests that use of VP-16 during the first hour of Ara-C administration produces a higher cell kill in vitro (E. Cadman and C. Benz, personal communication). Daily VP-16 scheduling was not employed in an effort to design a regimen that did not require prolonged hospitalization and did not have excessive marrow toxicity. Further pharmacologic studies to optimize Ara-C-VP-16 interaction and to explore the use of high-dose methotrexate with these drugs should be pursued.

REFERENCES

1. LAWRENCE J, COLEMAN M, ALLEN SC, ET AL. Combination chemotherapy of advanced diffuse histiocytic lymphoma with the six-drug COP BLAM regimen. Ann Intern Med 97:190-195, 1982.
2. SKARIN AT, CANELLOS GP, ROSENTHAL DS, ET AL. Improved prognosis of diffuse histiocytic and undifferentiated lymphoma by use of high dose methotrexate alternating with standard agents (M-BACOD). J Clin Oncol 1:91-98, 1983.
3. KANTARJIAN H, BARLOGIE B, PLUNKETT W, ET AL. High dose cytosine arabinoside in non-Hodgkin's lymphoma. J Clin Oncol 1:684-694, 1983.
4. CAVALLI F, JUNGI WF, NISSER NI, ET AL. Phase II trial of *cis*-dichlorodiammineplatinum(II) in advanced malignant lymphoma. Cancer 48:1927-1930, 1981.

5. TAYLOR RE, MCELWAIN TJ, BARRETT A, ET AL. Etoposide as a single agent in relapsed advanced lymphomas—a phase II study. Cancer Chemother Pharmacol 7:175-177, 1982.
6. RIVERA G, DAHL GV, BOWMAN WP, ET AL. VM-26 and cytosine arabinoside combination chemotherapy for initial induction failure in childhood lymphocytic leukemia. Cancer 46:1727-1730, 1980.
7. MORTIMER J, BUKOWSKI RM, MONTIE J, ET AL. VP-16-213, *cis*-platinum, and adriamycin salvage therapy of refractory and/or recurrent nonseminomatous germ cell neoplasms. Cancer Chemother Pharmacol 7:215-218, 1982.
8. WHITE JC, HINES LH, and RATHMELL JP. Inhibition of 1-β-D-arabinofuranosylcytosine transport and not accumulation by teniposide and etoposide in Ehrlich ascites cells and human leukemic blasts. Cancer Res 45:3070-3075, 1985.

Mitomycin and Mitoxantrone in Previously Treated Patients With Advanced Breast Cancer[1]

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A total of 56 heavily pretreated patients with advanced breast cancer were treated with the combination mitomycin and mitoxantrone. Partial responses were seen in ten of 56 patients (18%), or ten of 44 (23%) completing two courses, while 18 (32%) had stable disease. Responses were seen in eight patients failing doxorubicin. The median duration of response was 26 weeks, with responders surviving a median of 37 weeks. A total of 59% of the courses were associated with World Health Organization grade 3 or 4 neutropenia ($< 1.0 \times 10^9$ cells/L). Nausea and vomiting were minimal. Mitomycin and mitoxantrone has activity in heavily pretreated patients with advanced breast cancer. [Cancer Treat Rep 71:191-193, 1987]

Mitoxantrone is an anthracenedione derivative developed by American Cyanamid. It was synthesized after Adamson (1) proposed that deletion of the amino sugar of anthracycline antibiotics may reduce cardiotoxicity. Mitoxantrone showed significant activity against murine tumor screens (2) and against breast cancer in phase II clinical trials (3). In phase I and II trials, mild nausea and vomiting occurred in approximately 20% of the patients and alopecia occurred in 10%. These minimal side effects make this drug attractive for palliative therapy in advanced breast cancer.

METHODS AND PATIENTS

Patients with advanced progressing, previously treated breast cancer were eligible. Patients had either received prior doxorubicin and cyclophosphamide or CMFP (cyclophosphamide, methotrexate, 5-fluorouracil, and prednisolone). Patients with measurable lesions were preferred. Eligible patients had Eastern Cooperative Oncology Group (ECOG) performance status of < 3, a life expectancy of > 12 weeks, no chemotherapy or radiotherapy in the preceding 3 weeks, and adequate peripheral blood counts. Patients with significant cardiac disease were excluded. Dose-finding occurred with the initial starting dose; mitomycin, 15 mg/m^2 iv Days 1 and 42 and mitoxantrone, 10 mg/m^2 iv Days 1, 21, 42, and 63. Response assessment occurred after two courses of mitomycin and mitoxantrone (MCN) (mitomycin, two doses; mitoxantrone, four doses) at 12 weeks. Responses were defined using standard criteria (4) such as a $\geq$ 50% reduction in the products of diameters for a partial response (PR) in measurable lesions. Weekly blood counts were performed to obtain accurate hematologic nadirs. Serial resting isotope left ventricular ejection fractions (LVEF) were performed every 6 weeks.

RESULTS

Fifty-nine eligible patients were entered on this study. Three patients were lost to follow-up after the first dose of MCN leaving 56 evaluable patients. The median age was 53 years, ECOG performance status was < 2 in 70% of the patients, most had had prior localized chest wall radiation therapy, and 46% had more than two prior endocrine therapies. All patients had had prior chemotherapy and 71% had failed a prior doxorubicin and cyclophosphamide combination after a mean doxorubicin dose of 250 mg/m^2 (range, 75-520).

Six patients had mitomycin, 15 mg/m^2, and mitoxan-

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trone, 10 mg/m^2; three had 15 mg/m^2 and 8 mg/m^2, and 47 had 10 mg/m^2 of each drug. Of 56 evaluable patients, 10 (18%) achieved a PR, 18 (32%) had stable disease, and 28 (50%) had progressive disease. Twelve patients received only the first part of the first course (one dose of both mitomycin and mitoxantrone). Six of these patients died of disease within 4 weeks of starting therapy; three had disease progression 1-3 weeks after starting therapy, and three refused further therapy. Thus, PR was seen in ten of 44 patients (23%) who completed two courses of MCN and were fully evaluable at 12 weeks. All responding patients were reassessed clinically and with abnormal pretreatment investigations at 12 weeks. Two further clinical PRs occurred lasting < 12 weeks but were not included in our responders. Two of 15 patients pretreated with CMFP alone and eight of 41 (20%) pretreated with doxorubicin and cyclophosphamide responded to MCN. Responses were seen at each dose level and at each major metastatic site. Complete responses were seen at all sites with the exception of bone.

The median duration of PR was 26 weeks (range, 12-33+). The median time to disease progression (PR plus stable disease) was 19 weeks (range, 7-37). The median survival was 24 weeks (range, 2-66+). The median survival for responders was 46 weeks; 36 weeks for patients with stable disease, and 6 weeks for patients with progressive disease.

A median of two courses of MCN (two doses of mitomycin and four doses of mitoxantrone) were given. More than 80% of the projected optimal dose was delivered in 74% of mitomycin courses, but in only 47% of mitoxantrone courses, since the latter drug was frequently omitted because of neutropenia.

Gastrointestinal toxicity was minimal with no nausea in 56% of courses and mild nausea (grade 1) in 20%. Mild stomatitis occurred in six courses. Of 37 patients evaluable for alopecia, 86% had no hair loss. Neutropenia was the major toxicity with 59% of all courses, and 67% of first courses, associated with World Health Organization grade 3 or grade 4 neutropenia ($< 1.0 \times 10^9$ cells/L). Four of six patients treated with MCN, 15 mg/m^2 and 10 mg/m^2, had grade 4 neutropenia. Three patients treated with MCN, 15 mg/m^2 and 8 mg/m^2, experienced grade 2 neutropenia with their first course. Two patients developed infections while neutropenic but no patient died of infection. Conversely, 64% of courses resulted in no thrombocytopenia, 14% resulted in grade 1 ($75-100 \times 10^9$ cells/L), and 14% resulted in grade 2 ($50-74.9 \times 10^9$ cells/L) thrombocytopenia.

At least two resting LVEF were performed in 28 patients. In 23 patients, the LVEF was unchanged (within 10% of baseline); in two, LVEF increased by $> 10\%$, and in three, LVEF decreased by $> 10\%$. In the latter patients, one had received 477 mg/m^2 of doxorubicin and 27.5 mg/m^2 of mitoxantrone, and two had received 40 mg/m^2 and 50 mg/m^2 of mitoxantrone. One further patient developed mild congestive heart failure after 520 mg/m^2 of prior doxorubicin and 24 mg/m^2 of mitoxantrone after serial LVEF had dropped 6% below the pre-MCN level. This patient responded to failure therapy and remained asymptomatic from her cardiac disease.

DISCUSSION

MCN is an active combination in patients who have progressive breast cancer after initial chemotherapy. PR was seen in eight of 41 patients (20%) who had previously progressed on doxorubicin and cyclophosphamide including those who had not responded to doxorubicin initially.

Our PR rate is similar to pooled data for mitomycin as a single agent (5), and thus may reflect mitomycin effect alone. However, in contrast to pooled data, we required PR in the majority of lesions at a majority of sites for at least 12 weeks. Two extra PRs lasting < 12 weeks were excluded. In addition, other studies with mitomycin alone produced PR in only 0%-16% of the patients (6,7). However, our PR rate appears inferior to the 35%-40% achieved with mitomycin and vinblastine or vindesine (8,9).

Neutropenia was the major toxicity, but was not a major clinical problem since only two patients became infected. The projected optimal dose of mitoxantrone was not achieved in most patients because of neutropenia, which may have limited the program's efficacy. A schedule with dosing every 4 weeks may be better tolerated and allow more mitoxantrone to be delivered. Responses were seen at each dose level, so that a mitomycin dose of 15 mg/m^2 and a mitoxantrone dose of 8 mg/m^2 may result in less neutropenia for similar efficacy. Patients accepted this program well because the nausea, vomiting, and alopecia were minimal. The cardiotoxicity identified in this predominantly anthracycline pretreated group was minimal. We may have avoided cardiac complications by arbitrarily stopping MCN when LVEF dropped to 10% of the baseline.

REFERENCES

1. ADAMSON RH. Daunomycin (NSC-82151) and Adriamycin (NSC-123127): a hypothesis concerning antitumor activity and cardiotoxicity. Cancer Chemother Rep 58:293-294, 1974.
2. WALLACE RE, MURDOCH KC, ANGIER RB, ET AL. Activity of a novel anthracenedione, 1, 4 dihydroxy 5, 8 bis ((2((2 hydroxyethyl) amino) ethyl) amino) 9, 10 anthracenedione dihydrochloride against experimental tumours in mice. Cancer Res 39:1570-1574, 1981.
3. YAP HY, BLUMENSCHEIN GR, SCHOLL FL, ET AL. Dihydroxyanthracenedione: a promising new drug in the treatment of metastatic breast cancer. Ann Intern Med 95:654-697, 1981.
4. MILLER AB, HOOGSTRATEN B, STAQUET M, ET AL. Reporting results of cancer treatment. Cancer 47:207-214, 1981.
5. HOOGSTRATEN B, and FABIAN C. A reappraisal of single drugs in advanced breast cancer. Cancer Clin Trials 2:101-109, 1979.
6. LOPEZ M, PAPALDO P, DI LAURO L, ET AL. Mitomycin C in patients with metastatic breast cancer refractory to hormone therapy and chemotherapy. Oncology 40:24-47, 1983.
7. CREECH RH, CATALANO RB, SHAH MK, ET AL. A phase II study of low dose mitomycin C in breast cancer. Proc Am Assoc Cancer Res and ASCO 22:439, 1981.

8. KONITS PH, AISNER J, VAN ECHO DA, ET AL. Mitomycin C and vinblastine chemotherapy for advanced breast cancer. Cancer 48: 1295–1298, 1981.

9. GAREWAL HS, BRESKS RJ, JONES SE, ET AL. Treatment of advanced breast cancer with mitomycin C combined with vinblastine or vindesine. J Clin Oncol 1:12, 772–775, 1983.

BRIEF REPORTS

Cross-Resistance of Menogaril and Mitoxantrone in a Subline of P388 Leukemia Resistant to Doxorubicin[1,2]

Bangaru Chandrasekaran, John Dimling, and Robert L. Capizzi[3,*]

Mice bearing the P388/S or P388/ADR (doxorubicin-resistant) leukemia were treated with menogaril or mitoxantrone. Both drugs were highly effective against P388/S but were ineffective against the doxorubicin-resistant subline, indicating cross-resistance. These observations may be of use in the design of clinical trials with these drugs. [Cancer Treat Rep 71:195-196, 1987]

While doxorubicin is one of the most effective antineoplastic drugs in clinical use, the major limitation to its protracted use is cardiotoxicity. In the search for new drugs possessing equal or greater antitumor activity but less cardiotoxicity than doxorubicin, a series of analogs have been synthesized. Two of these, menogaril and mitoxantrone, have entered clinical trial (1,2).

Laboratory studies suggest that menogaril or mitoxantrone act through a mechanism which differs from doxorubicin since, at lethal doses, menogaril binds weakly to DNA and minimally inhibits DNA and RNA synthesis in contrast to doxorubicin (3). Mitoxantrone binds to DNA by a nonintercalative, electrostatic interaction and induces non-protein-associated DNA strand breaks (4). Additionally, cells in S phase were more sensitive to doxorubicin as compared to maximum toxicity of menogaril to cells in G_1 (5) and mitoxantrone to cells in G_1 and G_2 (6). These differences between doxorubicin, menogaril, and mitoxantrone suggested a study of cross-resistance.

MATERIALS AND METHODS

A subline of P388 leukemia resistant to doxorubicin was the gift of Dr. D. Griswold, Southern Research Institute, Birmingham, AL. Mitoxantrone and menogaril were gifts from Lederle Laboratories, Wayne, NJ, and Upjohn Co, Kalamazoo, MI, respectively. Doxorubicin was obtained from Adria Laboratories Inc, Columbus, OH.

Female DBA_2 and AKD_2F_1 mice about 9-12 weeks old (Jackson Laboratories, Bar Harbor, ME) and weighing approximately 25 g were fed Purina mouse chow ad libitum. Doxorubicin (1 mg/ml in 0.9% NaCl), menogaril (2.25 mg/ml in 0.1 M acetic acid), and mitoxantrone (0.5 mg/ml in 0.9% NaCl) were sterilized by passing through 0.2-μm membrane and kept frozen between uses.

P388/ADR and P388/S (murine leukemia resistant and sensitive to doxorubicin, respectively) were maintained in exponential growth as an ascites tumor in DBA_2 mice by serial passages of 10^6 cells ip on a weekly basis. Resistance to doxorubicin in the P388/ADR subline was maintained by injecting doxorubicin (4 mg/kg) ip on Day 2 after inoculation of P388/ADR cells.

Experimental groups consisted of a minimum of seven tumor-bearing (10^6 cells ip) AKD_2F_1 mice. Three days after tumor implantation, each group received one of four treatments: menogaril (9.0 mg/kg), mitoxantrone (2 mg/kg), 0.1 M acetic acid only, or 0.9% NaCl only. These dosages were approximately the 0.7 LD10 doses for each drug. Drugs were administered ip into mice daily for 4 days in a volume of 0.1 ml.

The mice were observed daily until death. The percentage increase in life span (% ILS) was determined by comparison of the mean survival of treated mice with the mean survival of the appropriate control group. Toxicity was measured as weight loss during and after therapy and also as mean life span compared to control.

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TABLE 1.—Effect of menogaril or mitoxantrone on mice bearing P388 leukemia resistant and sensitive to doxorubicin

		P388/S*			P388/ADR*		
Group	Treatment†	Mean survival time (days ± SD)	% ILS	Maximum change in body weight‡ (%)	Mean survival time (days ± SD)	% ILS	Maximum change in body weight‡ (%)
1	0.9% NaCl	10 ± 1	—	9.4	10.6 ± 1.5	—	12.2
2	0.1 M acetic acid	9.3 ± 0.9	—	8.7	9.9 ± 1.2	—	7.1
3	Doxorubicin (4 mg/kg)	19.6 ± 4.6	96	−11.2	10.5 ± 1.5	—	11.6
4	Menogaril (9.0 mg/kg)	31 ± 2.9	233	−15.4	9.1 ± 0.9	−8	−3.3
5	Mitoxantrone (2.0 mg/kg)	29.6 ± 4.5	196	−12.1	10.9 ± 1.7	3	−5.3

*Murine P388 leukemia sensitive to doxorubicin (P388/S) and murine leukemia resistant to doxorubicin (P388/ADR).

†Mice were inoculated with 10^6 P388/S or P388/ADR murine leukemia cells ip 72 hrs before drug administration. Each group contained 7 mice. Group 1 is the control for Group 5 and Group 2 is the control for Group 4. Groups 2–5 of P388/ADR mice were treated with a single dose of doxorubicin (4 mg/kg) on Day 2 to maintain resistance. All treatments except doxorubicin were administered on Days 3–6 after tumor implantation, whereas doxorubicin (4 mg/kg) was administered ip as a single dose on Day 2.

‡Mean difference in body weights of mice in % between Day 0 and Day 7 postinoculation of tumor cells. % ILS of drug treated P388/S was statistically significant ($P = < 0.001$) against its respective control and similarly treated P388/ADR cells.

RESULTS AND DISCUSSION

The effect of menogaril or mitoxantrone on mice bearing the P388/S and P388/ADR leukemia is shown in table 1. Menogaril resulted in a 233% ILS in mice bearing P388/S and −8% ILS in mice bearing P388/ADR. Similarly, mitoxantrone caused a 196% ILS in mice bearing P388/S and a 3% ILS in mice bearing P388/ADR. These results suggest complete cross resistance (< 25% ILS) between menogaril, mitoxantrone, and doxorubicin in P388/ADR leukemia. The growth kinetics and lethality of P388/S and P388/ADR were virtually identical with the doubling around 18 hours (data not reported) and similar mean survival times.

While there was a steady increase in body weight of control mice, menogaril caused a 15.4% and 3.3% weight loss in mice bearing P388/S and P388/ADR leukemia, respectively. Similar effects were observed in mitoxantrone-treated mice, with a 12.1% and 5.3% decrease of weight in mice bearing P388/S and P388/ADR leukemia, respectively. The lesser weight loss in mice bearing the P388/ADR tumor was due to the accumulation of ascites fluid prior to death. Most of the drug-treated mice recovered their pretreatment weights by Day 9 postinoculation of tumor cells. None of the mice died from drug toxicity.

While the precise mechanism(s) of action of the anthracycline antibiotics is not fully elucidated, suggested mechanisms of cytotoxicity from doxorubicin include intercalation of the aglycone moiety between base pairs and noncovalent interaction with the phosphate backbone of DNA and generation of free radicals which may damage the mitochondrial membrane (7,8). At lethal doses, doxorubicin binds tightly to DNA and inhibits DNA and RNA synthesis in contrast to menogaril and mitoxantrone, which bind weakly to DNA and RNA and minimally inhibit DNA and RNA synthesis (3,5,6). However, the precise mechanism is not clear. Whatever the difference in biochemical mechanisms of action between doxorubicin, menogaril, and mitoxantrone, the P388/ADR leukemia is cross-resistant to all of these drugs. This cross-resistance may be important in clinical trials if patients are treated with menogaril or mitoxantrone following failure of doxorubicin and possibly other agents noted in pleiotropic drug resistance (9).

REFERENCES

1. FUJIMOTO S, and OGAWA M. Antitumor activity of mitoxantrone against murine experimental tumors: comparative analysis against various antitumor antibiotics. Cancer Chemother Pharmacol 8:137–162, 1982.
2. BHUYAN BK, ZIMMER DM, MAZUREK JH, ET AL. Comparative genotoxicity of Adriamycin and menogaril, two anthracycline antitumor agents. Cancer Res 43:5293–5297, 1983.
3. LI LH, KUENTZEL SL, MARCH LL, ET AL. Comparative biological and biochemical effects of nogalamycin and its analogs on L1210 leukemia. Cancer Res 39:4816–4822, 1979.
4. ALBERTS DS, PENG YM, BOWDEN T, ET AL. Pharmacology of mitoxantrone: mode of action and pharmacokinetics. Invest New Drugs 3:101–107, 1985.
5. BHUYAN BK, BLOWERS CL, and SHUGARS KD. Lethality of nogalamycin analogs and adriamycin to cells in different cell cycle phases. Cancer Res 40:3437–3442, 1980.
6. KIMLER BF, and CHENG CC. Comparison of the effects of dihydroxyanthraquinone and adriamycin on the survival of cultured Chinese hamster cells. Cancer Res 42:3631–3636, 1982.
7. TARAKHOVSKI AM, ZHMAREVA EN, and ROMODANO SA. Role of the system for superoxide radical formation and detection in the mechanism of the antitumor effect of Adriamycin. B Exp B Med 96:1596–1597, 1983.
8. GOORMAGHTIGH E, POLLAKIS G, PARAET M, ET AL. Free radicals formation and membrane damages induced by Adriamycin in mitochondria: a study in vivo and in vitro. Arch I Phys 92:BP12–B13, 1984.
9. LING V, and THOMPSON LH. Reduced permeability in CHO cells as a mechanism of resistance to colchicine. J Cell Physiol 83:103–116, 1974.

BRIEF REPORTS

Phase II Trial of Carboplatin in Patients With Advanced Germ Cell Tumors Refractory to Cisplatin[1,2]

Robert J. Motzer, George J. Bosl,* Kurt Tauer, and Robert Golbey[3]

A phase II trial of carboplatin was conducted in 22 patients with advanced germ cell tumors refractory to cisplatin-based chemotherapy. Twenty of 22 patients were evaluable for toxicity and response. Two partial responses and one minor response were seen. The major toxic effect was myelosuppression. Carboplatin has antitumor activity in patients with advanced germ cell tumors refractory to cisplatin, and phase II and III studies of combination chemotherapy are indicated. [Cancer Treat Rep 71:197-198, 1987]

Cisplatin has assumed a major role in the treatment and curability of germ cell tumors (GCT) (1,2). Toxicity of cisplatin includes renal, auditory, and gastrointestinal toxic effects (3). Patients who fail to achieve a complete response (CR) with conventional cisplatin-based regimens rarely achieve a CR with cisplatin-based salvage therapy (4). Carboplatin (CBDCA) is a second-generation cisplatin analog with lesser nephrotoxicity when compared to cisplatin (5,6), activity in patients with ovarian cancer heavily pretreated with cisplatin (7), and ease of administration in an outpatient setting. This study evaluated the effectiveness of CBDCA in the treatment of patients with refractory GCT.

PATIENTS AND METHODS

All patients had histologically confirmed GCT, failure to achieve CR with conventional cisplatin-based therapy and progressive disease at the time of treatment, bidimensionally measurable disease, estimated life expectancy > 8 weeks, Karnofsky performance status $> 50\%$, wbc count $> 4000/mm^3$, platelet count $> 100{,}000/mm^3$, BUN < 30 mg/dl, and serum creatinine < 1.5 mg/dl or creatinine clearance > 50 ml/minute/1.73 m^2. No patients had received myelosuppressive chemotherapy within 4 weeks of starting CBDCA.

The starting dose of CBDCA was 350 mg/m^2 administered as a single iv bolus every 28 days. Patients with a pretreatment platelet count of 100,000-150,000/mm^3 or a history of severe myelosuppression were started at 250 mg/m^2; 500 ml of 5% dextrose in 0.45% NaCl was given iv before and after treatment. In the absence of demonstrable hematologic toxicity, subsequent doses were escalated by 50 mg/m^2. If the wbc or platelet count nadir was $< 2000/mm^3$ or $< 50{,}000/mm^3$, respectively, then subsequent doses of CBDCA were decreased by 50 mg/m^2.

Measurable disease was evaluated every 4 weeks. Therapy was continued until progression of disease or surgical intervention.

RESULTS

Twenty of the 22 patients treated with CBDCA were evaluable for response and toxicity. The two inevaluable patients had early deaths. Patient characteristics are listed in table 1. Dose escalation was possible in nine patients. Two patients had partial responses (PRs) and one a minor response (MR). One patient with a PR received three cycles of CBDCA and had disappearance of left pulmonary nodules and a $> 50\%$ reduction of right pulmonary nodules accompanied by a decline in alphafetoprotein (AFP) from an initial value of 13,110 to a value of 153 ng/ml. He underwent a resection of residual tumor. This patient's AFP did not normalize, and pulmonary nodules reappeared 3 months later. The second PR was seen after four cycles of CBDCA. Total resolution of pulmonary nodules, $> 75\%$ reduction in a retroperitoneal mass on computerized tomographic (CT) scan, and normalization of initially elevated AFP were

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observed. At exploratory laparotomy, the abdominal mass was unresectable and was implanted with ^{125}I seeds. The MR consisted of resolution of supraclavicular adenopathy of < 4 weeks' duration in a patient with seminoma.

Toxicity was mild (table 2). Myelosuppression was the major toxic effect. The median wbc and platelet count nadirs were 4.0 and 101,000/mm^3, respectively. Dose reduction and prophylactic platelet transfusions were required in one patient, for a platelet count of 2000/mm^3. No patients required hospitalization for neutropenic fever. One patient had a rise in serum creatinine > 0.5 mg/dl. Nausea and vomiting were generally confined to the day of treatment and minimized by the administration of metoclopramide, dexamethasone, and diphenhydramine.

TABLE 2.—Toxicity of CBDCA

Toxic effect	No. of patients
Wbc count nadir (/mm^3)	
> 3000	15
2000–3000	4
1000–2000	1
< 1000	0
Platelet count nadir (/mm^3)	
> 150,000	6
100,000–150,000	6
50,000–100,000	6
20,000–50,000	0
1,000–20,000	2
Nausea and vomiting	15
Renal insufficiency*	1
Alopecia	0
Ototoxicity (subjective)	0

*Increase in serum creatinine > 0.5 mg/dl.

DISCUSSION

CBDCA was well tolerated, with little nonhematologic toxicity. Myelosuppression was the major toxic effect, but despite extensive previous myelosuppressive therapy, no patients required hospitalization. Dose escalation was possible in nine of 16 patients who were initially treated at the 350-mg/m^2 dose level. The two PRs and one MR which were observed were dramatic and surprising, given the extent of prior treatment. These results indicate that CBDCA is active in some patients with GCT no longer responsive to cisplatin. Phase II and III studies of combination therapy are indicated.

TABLE 1.—Characteristics of patients treated with CBDCA

Characteristic	No. of patients
Entered	22
Evaluable	20
Median age in yrs (range): 24 (17–58)	
Median Karnofsky performance status (range): 80 (60–90)	
Histology	
Seminoma	1
Nonseminomatous GCT	19
Primary site	
Testis	17
Retroperitoneum	2
Mediastinum	1
Prior chemotherapy*	
VAB-6 + etoposide/cisplatin (refs 1, 4, 8)	17
PVB + etoposide/cisplatin (refs 2, 4)	1
Other cisplatin-based therapy + etoposide/cisplatin (ref 4)	2
Status at time of treatment with CBDCA	
Relapse from CR to cisplatin-based therapy	1
Progression on cisplatin-based therapy	19
Initial dose CBDCA (mg/m^2)	
250	4
350	16
Dose escalation (mg/m^2)	
400	9
450	3
500	1

*VAB-6 = vinblastine, dactinomycin, cyclophosphamide, bleomycin, and cisplatin; PVB = cisplatin, vinblastine, and bleomycin.

REFERENCES

1. Vugrin D, Herr HW, Whitmore WF, et al. VAB-6 combination chemotherapy in disseminated cancer of the testis. Ann Intern Med 95:59–61, 1981.
2. Einhorn LH. Testicular cancer as a model for a curable neoplasm. The Richard Rosenthal Foundation Award Lecture. Cancer Res 41: 3275–3280, 1981.
3. Von Hoff DD, Schilsky R, Reichert CM, et al. Toxic effects of *cis*-dichlorodiammineplatinum(II) in man. Cancer Treat Rep 63:1527–1531, 1979.
4. Bosl GJ, Yagoda A, Golbey RB, et al. Role of etoposide-based chemotherapy in the treatment of patients with refractory or relapsing germ cell tumors. Am J Med 78:423–428, 1985.
5. Calvert AH, Harland SJ, Newell DR, et al. Early clinical studies with *cis*-diamine-1,1 cyclobutane dicarboxylate platinum II. Cancer Chemother Pharmacol 9:140–147, 1982.
6. Curt GA, Arygiel JJ, Corden BJ, et al. A phase I and pharmacologic study of diaminecyclobutane-dicarboxylatoplatinum. Cancer Res 43:4470–4473, 1983.
7. Evans BD, Raju KS, Calvert AH, et al. Phase II study of JM8, a new platinum analog in advanced ovarian carcinoma. Cancer Treat Rep 67:997–1000, 1983.
8. Leitner SP, Israel A, and Bosl GJ. Treatment of poor prognosis germ cell tumors with alternating cycles of VP-16/cisplatin and VAB-6. Proc ASCO 4:104, 1985.

BRIEF REPORTS

Pilot Study of Cyclophosphamide Plus Carboplatin in Advanced Ovarian Carcinoma[1,2]

J. H. Edmonson,[3,*] G. W. McCormack,[4] J. E. Krook,[4] H. J. Long,[3] J. A. Jefferies,[3] and R. L. Richardson[3]

Six patients with histologically proven stage III–IV ovarian carcinoma received carboplatin (CBDCA) (150 mg/m^2) plus cyclophosphamide (1000 mg/m^2) monthly for 1 year unless disease progressed earlier. Six other patients received CBDCA (225 mg/m^2) with the same cyclophosphamide dose monthly. Continued treatment with the higher CBDCA dose was not tolerable because of myelosuppression, but no other dose-limiting toxic effect was observed. Complete tumor regression was proven at secondary laparotomy in six of the 12 patients, and five of these remain disease-free from 26+ to 28+ months after beginning chemotherapy. Four of these five patients received the higher CBDCA dose. [Cancer Treat Rep 71:199-200, 1987]

Following the demonstration by Evans et al (1) that carboplatin (CBDCA) was therapeutically comparable to cisplatin (CDDP) as a single agent in the treatment of ovarian carcinoma we decided to study CBDCA since we had earlier studied CDDP in combination with cyclophosphamide (Cyclo) (2). We reasoned that if Cyclo-CBDCA was therapeutically as successful as Cyclo-CDDP, it might provide a treatment with a superior therapeutic index because of the lesser emetogenic potential and minimal nephrotoxicity and neurotoxicity of CBDCA. Utilizing the same doses of Cyclo used in our previous studies we have performed a dose-seeking study of CBDCA for use in a Cyclo-CBDCA combination regimen.

MATERIALS AND METHODS

Between February and September 1984, ten patients with histologically confirmed stage III–IV epithelial ovarian carcinoma without prior chemotherapy and two with prior melphalan began treatment. All of the patients had satisfactory bone marrow, liver, and kidney functions as indicated by leukocyte and platelet counts of at least 4000 and 130,000/μl, respectively, normal serum bilirubin, and normal creatinine levels. No bedridden patients were accepted. Chemotherapy was begun as soon as patients had recovered from primary abdominal exploration. All patients received Cyclo (1000 mg/m^2) plus CBDCA at doses of either 150 mg/m^2 (six patients) or 225 mg/m^2 (six patients) given iv on Day 1 of each monthly treatment cycle. Cyclo was administered in 250 mg of 5% dextrose in water over 15 minutes followed immediately by injection of CBDCA via the same iv. Doses of both cytotoxic agents were reduced if leukocyte or platelet count nadirs fell to < 1500 and 75,000/μl, respectively. Treatment was continued for 1 year in the absence of disease progression, and those patients without clinically overt disease received second-look laparotomy. Objective tumor responses to treatment were defined clinically in those patients with overt clinical progression and at surgery in those receiving secondary exploration. Biopsy proof of disease-free status at second-look laparotomy was required to define complete tumor regression (CR). Partial regression (PR) was defined as the disappearance during treatment of at least half of the tumor present at the beginning of treatment. This was judged by surgical findings if secondary laparotomy was done.

RESULTS

Six of the 12 patients achieved CR (negative second-look laparotomies), two achieved PRs, and three had stable disease for 6, 9, and 12 months, respectively (table 1). One patient experienced immediate progression of disease after the initial course.

Mean leukocyte count nadirs including all courses were 1250 and 1000/μl for the groups of six patients, respectively, beginning at 150- and 225-mg/m^2 doses of CBDCA. Overall mean platelet count nadirs for these

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TABLE 1.—Patients treated with Cyclo-CBDCA

						Wbc count nadir $(\times 10^3/\mu l)$		Platelet count nadir $(\times 10^3/\mu l)$				
Age (yrs)	Prior therapy	Extent of disease*	Disease stage	Tumor grade (1-3)	CBDCA dose (mg/m^2)	1st course	Any course	1st course	Any course	Best response	Second-look laparotomy	Current status†
73	No	Minimal	III	2	150	3.0	1.6	161	121	CR	Negative	Alive, NED on Day 837
69	No	Extensive	III	2	150	1.6	—	257	—	Disease progression	—	Died on Day 174
57	No	Extensive	IV	2	150	2.5	1.5	205	116	Stable disease	Positive	Died on Day 389
53	No	Minimal	III	2	150	1.7	0.8	106	78	Stable disease	Positive	Alive with disease on Day 888
64	Yes	Extensive	III	2	150	1.9	1.8	204	166	CR	Negative	Died on Day 714
82	Yes	Extensive	III	2	150	0.3	0.3	23	23	PR	Positive	Died on Day 362
60	No	Extensive	III	2	225	3.6	1.6	132	58	CR	Negative	Alive, NED on Day 833
67	No	Extensive	III	3	225	0.6	0.6	221	154	CR	Negative	Alive, NED on Day 794
57	No	Extensive	III	2	225	1.8	1.3	225	158	Stable disease	Positive	Died on Day 396
68	No	Massive	III	2	225	1.1	0.9	59	59	PR	—	Alive with disease on Day 822
63	No	Minimal	III	3	225	0.9	0.9	34	34	CR	Negative	Alive, NED on Day 825
72	No	Minimal	III	3	225	1.0	1.0	200	65	CR	Negative	Alive, NED on Day 841

*Minimal = no mass remaining after pretreatment cytoreductive surgery > 2 cm in longest diameter; Extensive = masses > 2 cm in diameter present, but total residual tumor volume estimated to be ≤ 250 ml; and massive = residual tumor volume > 250 ml.

†NED = no evidence of disease.

two treatment groups were 113,000 and 86,000/μl, respectively. Reductions of doses of both drugs were required to alleviate myelosuppression in four of the six patients receiving CBDCA at doses of 150 mg/m^2 after a median of three courses. At the 225-mg/m^2 CBDCA doses all of the six patients required dosage reduction after a median of one course of chemotherapy and four patients in this group required further reduction later. Two of these patients required a third dose reduction. Patients initially receiving the 150-mg dose of CBDCA received from 46% to 100% (median, 80%) of the predicted total doses of both agents. Patients beginning treatment at the 225-mg dose of CBDCA actually received 38%-97% (median, 60%) of the full calculated doses of the two drugs based on the number of months in the study. Significant alopecia has been common (eight patients), and vomiting has occurred in all 12 patients (severe in six). No significant adverse renal or neurologic effects have been observed.

Seven of the patients were alive from 26+ to 29+ months after beginning treatment and five of these remained free of disease following negative second-look laparotomies.

DISCUSSION

With only 12 patients in the pilot study, no accurate assessment of the relative therapeutic worth of this two-drug combination can be given. We must, however, recognize it as active enough against ovarian carcinoma to consider it for further comparative studies.

With nearly 2.5 years of follow-up time since the last patient began treatment, the finding of five patients still free of disease recurrence is not completely unexpected. Perhaps more intriguing, however, is the observation that two patients who entered the study with extensive residual disease now remain disease-free. Four patients (including those two) receiving the higher (CBDCA) dose regimen and one receiving the lower dose regimen are currently disease-free. Despite the frequent need to reduce doses shortly after beginning therapy with the combination of Cyclo (1000 mg/m^2) and CBDCA (225 mg/m^2) monthly, this regimen might be more active against epithelial ovarian carcinoma than the lower-dose regimen.

REFERENCES

1. EVANS BD, CALVERT AH, HARLAN SJ, ET AL. Phase II and early phase III trials with JM8 (*cis*-diammine 1, 1-cyclo-butane dicarboxylate platinum II) in advanced ovarian carcinoma. Proc Am Assoc Cancer Res 24:154, 1983.
2. DECKER DG, FLEMING TR, MALKASIAN GD, ET AL. Cyclophosphamide plus cisplatinum in combination: treatment program for stage III or IV ovarian carcinoma. Obstet Gynecol 60:481-486, 1982.

BRIEF REPORTS

Etoposide in Combination With Cytarabine, Doxorubicin, and 6-Thioguanine for Treatment of Acute Nonlymphoblastic Leukemia in a Protocol Adjusted for Age[1]

Murray M. Bern,* Sabina R. Wallach, Charles F. Arkin, Jacob J. Lokich, Mark S. Huberman, Norwood R. Anderson, Joseph C. Corkery, Steven D. Paul, Donald F. Phillips, Henry A. Sonneborn, and Thomas E. Zipoli[2]

Etoposide combined with cytarabine, doxorubicin, and 6-thioguanine was used to treat 34 patients with acute nonlymphoblastic leukemia (ANLL) in an age-adjusted protocol, with patients > 50 years old receiving fewer days of therapy. Complete remissions (CR) occurred in 85% of all patients (29 of 34 patients). Patients ≤ 50 years of age achieved a 94% CR rate (17 of 18 patients) compared to a 75% CR rate (12 of 16 patients) in older patients. Duration of remission was less for those > 50 years of age. The remission rate for primary ANLL was 86% (19 of 22 patients) and for secondary or relapsed ANLL was 83% (ten of 12 patients). Thus, this is effective therapy for primary and secondary or relapsed ANLL. When the days of therapy are reduced for older patients' age, the remissions are fewer and less durable. [Cancer Treat Rep 71:201-203, 1987]

Etoposide (VP16-213) is active as a single agent in primary and resistant acute nonlymphoblastic leukemia (ANLL) (1-5). It was more effective in treating the monoblastic variant. The complete response (CR) rates using VP16-216 in combination programs and in a variety of dose schedules range from 0% to 65% in previously treated patients (1-10). This paper describes VP16-213 in a four-drug induction and maintenance regimen for primary and relapsed or secondary ANLL using dose stratification based on the patient's age.

METHODS

All patients with ANLL admitted between July 1, 1981, and May 1, 1984, are reported. ANLL was diagnosed by analysis of bone marrow and peripheral blood light microscopy, cytochemistry, and cell surface markers and was classified according to the French-American-British (FAB) system. Table 1 shows the VP16-213, cytarabine, doxorubicin, and 6-thioguanine (VATA) regimen. Maintenance therapy was given to all patients achieving CR who did not receive marrow transplantation and who had not previously received doxorubicin. Bone marrows were examined after each induction and every 3 months during maintenance. Thereafter, marrow examination was performed every 6 months or for peripheral blood abnormalities. Patients gave informed consent.

CR is defined as $< 5\%$ leukemic blast cells in the bone marrow and no leukemic blast cells in the peripheral blood. Partial remission (PR) is defined as 5%-20% blasts in the marrow and no leukemic blast cells in the peripheral blood. For CR and PR, the marrow cellularity was $> 50\%$, with normal peripheral blood cell counts, and no symptoms referable to leukemia. Duration of remission is measured from day of documented remission until November 15, 1985, or until the appearance of $> 5\%$ marrow blasts or any peripheral blood blast cells. Statistical analysis is based on the t test for independent samples.

RESULTS

Thirty-four patients received induction therapy (table 2). Sixteen of these 34 patients were > 50 years of age. Twelve patients had secondary or relapsed ANLL equally divided between the two age groups. Twenty-nine of the 34 patients (85%) achieved CR; one patient achieved PR. Eighteen CRs followed the first induction and 11 followed the second. Three of the five nonre-

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[1] Received Dec 17, 1985; revised Oct 14, 1986; accepted Oct 29, 1986.

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TABLE 1.—Drug, dose, and schedule for VATA induction and maintenance chemotherapy

Drug	Dose (mg/m^2/day)	Route	Days of therapy $\leq$ 50 yrs old	Days of therapy $>$ 50 yrs old
		Induction, 2 courses given 30 days apart		
VP16-213	50	Iv bolus	5	3
Cytarabine	75	Iv continuous infusion	7	5
6-Thioguanine	75	Oral twice/day	7	5
Doxorubicin	20	Iv bolus	3	2
		*Maintenance, 10 courses**		
VP16-213	40	Iv bolus	5	3
Cytarabine	66	Iv continuous infusion	5	3
6-Thioguanine	50	Oral twice/day	5	3
Doxorubicin	26	Iv bolus	1	1

*All drug doses were reduced by 1/3 if there were $< 1000/\text{mm}^3$ bands + PMNs and $< 75{,}000/\text{mm}^3$ platelets at the time of initiation of therapy.

sponding patients died of ANLL during induction. Four of the five nonresponders were $>$ 50 years of age. Thus, 94% of the patients (17 of 18) $\leq$ 50 years of age achieved CR (95% confidence limits, 83%–106%) and 75% (12 of 16) of those $>$ 50 years of age achieved CR (95% confidence limits, 52%–98%). For all patients $\leq$ 50 years old the median disease-free survival was 78 weeks, while it was 22 weeks for older patients ($P < 0.05$). For patients receiving maintenance therapy median disease-free survival was 108 weeks for younger patients but 36 weeks for older patients ($P < 0.05$) (fig 1). The FAB status had no detectable effect on outcomes.

Patients with relapsing or secondary ANLL had remission rates equal to those with primary ANLL, 83% (ten of 12 patients) and 86% (19 of 22 patients), respectively. Disease-free survival was comparable for both groups: median of 48 weeks (range, 10–180+) for primary ANLL and median of 52 weeks (range, 8–80) for secondary/relapsing ANLL.

The two induction courses were completed without dose modification, and 32 of 34 patients began the second course on schedule. Eleven younger patients and six older patients had a polymorphonuclear neutrophil count (PMN) $< 500/\text{mm}^3$ at diagnosis of leukemia. Days of leukopenia were fewer in the first course among the older patients (median, 12 days for older vs 20 days for younger). The duration of thrombocytopenia was equal in the groups. There were fewer days of fever following both induction courses in the older patients (median, 13 and 5 days for older vs 19 and 8 days for younger patients, respectively, for 1st and 2nd courses). Major complications were more frequent in the younger patients, including 14 of the 21 patients with bacteremias, two with fungemias, and two with *Aspergillus* pneumonias.

TABLE 2.—Patient characteristics*

Characteristic	$\leq$ 50 yrs old	$>$ 50 yrs old
No. of patients	18	16
Mean age in yrs (range)	31.7 (15–49)	64.0 (52–78)
Sex		
Male	11	6
Female	7	10
Disease status		
Primary ANLL	11	11
Relapsing ANLL	4	1
Secondary ANLL		
Dyspoietic marrow		2
Sideroblastic anemia	1	1
Blast crisis following chronic myeloblastic leukemia	1	
Hodgkin's disease		1
Non-Hodgkin's lymphoma	1	

*Unless otherwise specified, values = No. of patients.

DISCUSSION

Results of this four-drug therapy for ANLL are comparable to the best reported regimens in which VP16-213 was not included. Based on its activity as a single agent in the treatment of previously treated ANLL and also this study, VP16-213 is a reasonable agent to introduce into prospective comparative trials comparing VATA to previously established regimens not containing VP16-213. This combination with VP16-213 may have a unique role in the treatment of secondary or relapsed leukemias (10).

The optimal dose for VP16-213 in treating ANLL is not established. Most trials used 5 days of 50–100 mg/m^2. Based on cell cultures, L1210 mouse models, and limited clinical experiences, intermittent appears to be superior to infusion therapy (11,12). Very little is found in the cerebrospinal fluid after bolus therapy but more may accumulate with infusion therapy (13).

The influence of age on the outcome of intensive therapy as a single variable remains difficult to appraise in the midst of so many other variables (14–18). Patients $>$ 50 years of age can benefit from intensive therapy, but may be more vulnerable to the complications. In some reports, as in this one, being $\leq$ 50 years of age is a favor-

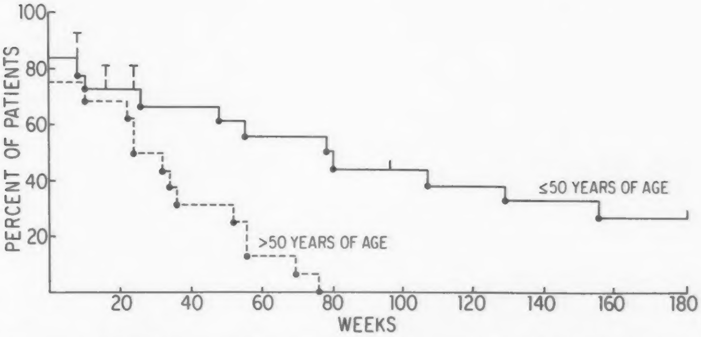

FIGURE 1.—Disease-free survival for all patients divided according to their being ≤ or > 50 yrs of age. T = transplant. PRs are indicated as failure to remit on the ordinate. The last patient to relapse at 160 wks had CNS disease only.

able factor for overall survival. In this age-stratified VATA protocol there is less drug-related morbidity and mortality in the older group. Unfortunately, the disease-free survival for the older patients is less than the more aggressively treated, younger patients. Thus, higher doses may create better antileukemic effects, but probably at the cost of greater morbidity and possibly mortality.

REFERENCES

1. SMITH IE, GERKEN ME, CLINK HM, ET AL. VP-16-213 in acute myelogenous leukemia. Postgrad Med J 52:66-70, 1976.
2. VAN ECHO DA, WIERNIK PH, and AISNER J. Reinduction therapy for relapsed acute non-lymphocytic leukemia (ANLL) patients. Proc Am Assoc Cancer Res and ASCO 19:144, 1978.
3. SCHMOLL H. Review of etoposide single-agent activity. Cancer Treat Rev 9(suppl A):21-30, 1982.
4. VARINI M, CAVALLI F, and SAUTER C. Etoposide in the treatment of acute leukemia in adults. Cancer Treat Rev 9(suppl A):59-62, 1982.
5. SHAW MJ. The distinctive features of acute monocytic leukemia. Am J Hematol 4:97-103, 1978.
6. JACOBS P, DUBOVSKY D, HONGAARD M, ET AL. Epipodophyllotoxin VP-16-213 in acute and non-lymphoblastic leukemia. Br Med J 1:396, 1975.
7. BERNASCONI C. Etoposide (VP16) in the treatment of monocytic leukemias. *In* Proceedings of the International Symposium "New Drugs of Cancer Treatment in the Eighties," Rome, Apr 10-11, 1981.
8. VAN ECHO DA, LICHTENFELD KM, and WIERNIK PH. Vinblastine, 5-azacytidine, and VP-16-213 therapy for previously treated patients with acute nonlymphocytic leukemia. Cancer Treat Rep 61:1599-1602, 1977.
9. SCHIFFER CA, DEBELLIS R, KASDORF H, ET AL. Treatment of the blast crisis of chronic myelogenous leukemia with 5-azacytidine and VP-16-213. Cancer Treat Rep 66:267-271, 1982.
10. BENNETT JM, LYMANN GH, CASSILETH PA, ET AL. A phase II trial of VP-16-213 in adults with refractory acute myeloid leukemia: an Eastern Cooperative Oncology Group study. Am J Clin Oncol 7:471-473, 1984.
11. VIETTI TJ, VALERIOTE FA, KALISH R, ET AL. Kinetics of cytotoxicity of VM-26 and VP-16-213 on L1210 leukemia and hematopoietic stem cells. Cancer Treat Rep 62:1313-1320, 1978.
12. DOMBERNOWSKY P, and NISSEN NI. Schedule dependency of the anti-leukemic activity of the podophyllotoxin derivative VP-16-213 (NSC-141540) in L1210 leukemia. Acta Pathol Microbiol Scand 81: 715-724, 1973.
13. HO DHW, KANELLOPOULOS KA, YAP HY, ET AL. Clinical pharmacology of etoposide by radioimmunoassay. Proc Am Assoc Cancer Res 24:131, 1983.
14. REIFFERS J, RAYNAL F, and BROUSTET A. Acute myeloblastic leukemia in elderly patients. Treatment and prognostic factors. Cancer 45:2816-2820, 1980.
15. CURTIS JE, MESSNER HA, HASSELBACK R, ET AL. Contributions of post and disease-related attributes to the outcome of patients with acute myelogenous leukemia. J Clin Oncol 2:253-259, 1984.
16. FOON KA, ZIGHELBAUM J, YALE C, ET AL. Intensive chemotherapy is the treatment of choice for elderly patients with acute myelogenous leukemia. Blood 58:467-470, 1981.
17. KAHN SB, BEGG CB, MAZZA JJ, ET AL. Full dose versus attenuated dose daunorubicin, cytosine arabinoside, and 6-thioguanine in the treatment of acute non-lymphoblastic leukemia in the elderly. J Clin Oncol 2:865-870, 1984.
18. BERN MM, CLOUD LP, CORKERY JC, ET AL. Age and treatment of acute non-lymphoblastic leukemia. N Engl J Med 305:642-643, 1981.

CLINICAL TRIALS SUMMARIES

Phase II Trial of Vindesine in Malignant Pleural Mesothelioma[1,2]

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Little information is available regarding the effectiveness of chemotherapeutic agents on malignant mesothelioma. Doxorubicin, considered at first to be the best single agent (1), has in fact poor activity (2). There are very few combination regimens, with or without doxorubicin, reported to be active (1). Though several drugs have shown some anecdotal activity, phase II trials are still necessary (3-5). Vindesine seemed to be worth trying in malignant mesothelioma, having induced significant rates of objective responses in several cancer types.

PATIENTS AND METHODS

Twenty-one patients were entered in this trial from November 1980 to June 1981 (table 1). A histopathologic diagnosis had been made by thoracotomy in 14 patients and by thoracoscopy in seven. A pleurodesis had been achieved in all patients. At the time of the assay all patients had progressive disease, and none had received prior chemotherapy.

Vindesine was administered by iv bolus injection at a dose of 2 mg/m^2/day for 2 consecutive days every 2 weeks. Doses were decreased by 50% in case of myelotoxicity or when moderate neurotoxicity was observed. Patients received at least three cycles to be evaluated (median, seven cycles).

Responses were evaluated monthly on serial x-rays by measuring the diameters of pleural masses previously documented as mesothelioma by thoracoscopy or thoracotomy. The response criteria used are the same as those published by Chahinian (1). In patients with progressive disease the drug was stopped after at least two cycles and continued until evidence of disease progression in the others.

RESULTS

We observed no objective responses. In the eight patients who had stable disease over a mean interval of 7.1 months, the mean number of cycles was 11.5 ± 3. Thirteen patients had progressive disease. Toxicity was mild; in one patient, however, peripheral neurotoxicity led to drug withdrawal after two courses.

DISCUSSION

This trial confirms the poor activity of vindesine in mesothelioma (3), since no objective responses were induced. The fact that in eight patients no measurable progression of the disease occurred over a mean period of 7 months might be related to the natural history of their mesothelioma. Conversely, this stabilization might be due to vindesine and would thus be worth considering in patients whose survival does not usually exceed 12-16 months.

TABLE 1.—Patient characteristics and response

Characteristic	No. of patients
Total	21
Sex	
Male	16
Female	5
Mean age in yrs (range): 62 (41-78)	
Karnofsky index: ≥ 60	
Histopathology	
Epithelial carcinoma	14
Mixed cell carcinoma	5
Fibrosarcoma	2
Stage*	
I (ipsilateral pleura)	12
II (ipsilateral lung or mediastinum)	4
III (contralateral extension)	5
IV (metastases)	0
Prior chemotherapy	0
Median No. of cycles/patient (range): 7 (2-24)	
Neurotoxicity	
Mild	8
Severe	1
Response	
Complete	0
Partial	0
Stable disease	8†
Progressive disease	13

*Butchart classification (6).
†Mean, 7.1 ± 1.6 mos.

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[1] Received Mar 28, 1986; revised Sept 4, 1986; accepted Sept 26, 1986.

[2] Supported by the Cercle d'Etude Pneumologique (*C. Boutin*, coordinator).

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REFERENCES

1. CHAHINIAN AP. Management of Pleural Tumors and Malignant Pleural Effusion. *In* The Pleura in Health and Disease (Chretien J, Bignon J, and Hirsch A, eds). New York, 1985, vol 30, pp 571-584.
2. SØRENSEN PG, BACH F, BORK E, ET AL. Randomized trial of doxorubicin versus cyclophosphamide in diffuse malignant pleural mesothelioma. Cancer Treat Rep 69:1431-1432, 1985.
3. KELSEN D, GRALLA R, CHENG E, ET AL. Vindesine in the treatment of malignant mesothelioma: a phase II study. Cancer Treat Rep 67:821-822, 1983.
4. HARVEY VJ, SLEVIN ML, PONDER BA, ET AL. Chemotherapy of diffuse malignant mesothelioma. Phase II trials of single-agent 5-fluorouracil and adriamycin. Cancer 54:961-964, 1984.
5. MINTZER DM, KELSEN D, FRIMMER D, ET AL. Phase II trial of high-dose cisplatin in patients with malignant mesothelioma. Cancer Treat Rep 69:711-712, 1985.
6. BUTCHART EG, ASHCROFT T, BARNSLEY WC, ET AL. Pleuropneumonectomy in the management of diffuse malignant mesothelioma of the pleura. Experience with 29 patients. Thorax 31:15-24, 1976.

CLINICAL TRIALS SUMMARIES

Therapy for Advanced Renal Cell Cancer With Spirogermanium: A Southwest Oncology Group Study[1,2]

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Spirogermanium, an investigational anticancer drug, is a member of a class of azaspirane compounds containing the metal germanium substituted for a 1-carbon moiety in the spirane structure, increasing the biologic activity of the compound (1,2). Although its mode of action has not been fully elucidated, it appears that spirogermanium is not a phase- or cell cycle-specific drug and that it inhibits DNA, RNA, and protein synthesis (2,3), with protein synthesis inhibition being the most significant (4).

Because of its demonstrated experimental antitumor activity and its lack of bone marrow toxicity (3,4), a study of spirogermanium in advanced renal cell carcinoma was initiated by the Southwest Oncology Group.

Eligibility requirements included histologically proven metastatic renal cell carcinoma, clearly measurable disease, life expectancy of at least 6 weeks, performance status < 2 by Southwest Oncology Group criteria, prior treatment with less than two chemotherapy regimens, and pretreatment creatinine and bilirubin < 2.0 mg/100 ml. Informed consent in accordance with institutional and Food and Drug Administration guidelines was required. Patient characteristics are shown in table 1.

Spirogermanium was administered at a dose of 80 mg/m^2 three times a week as an iv infusion over ≥ 60 minutes. The dose was escalated by 10 mg/m^2 each week to a maximum of 120 mg/m^2 if no CNS toxicity occurred. If CNS symptoms occurred, the dose was reduced or the time of infusion was lengthened. Treatment was continued until documented disease progression occurred. Twenty-eight days of treatment constituted an adequate trial. Standard response criteria were employed.

TABLE 1.—Patient characteristics

Characteristic	No. of patients
Eligible	32
Median age in yrs (range): 58 (35–80)	
Sex	
Male	18
Female	13
Median performance status (range): 1 (0–2)	
Prior treatment	
Surgery	25
Radiation therapy	13
Chemotherapy	14
Hormonal therapy	7
Chemotherapy and hormonal therapy	3
Interferon	3
Hormonal therapy and immunotherapy	1
No chemotherapy	9
Toxicity	
CNS	15
Nausea and vomiting	9
Stomatitis	2
Phlebitis	4
Neutropenia	2

Thirty-two patients were entered, with 26 being evaluable for response. The six unevaluable patients included three who refused further therapy, one early death unrelated to therapy, and two who had therapy discontinued because of toxicity (one with stomatitis and one with chemical phlebitis).

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[*] *Reprint requests to:* Southwest Oncology Group (SWOG-8218), Operations Office, 5430 Fredericksburg Rd, Suite 618, San Antonio, TX 78229.

Of the 26 evaluable patients, there were no complete or partial responses. One patient had reduction in size of some but not all lung lesions lasting 20 weeks, and five had stable disease from 10 to 24 weeks.

Toxicity was acceptable, with the most frequent toxic effects being CNS and/or gastrointestinal (table 1). The CNS symptoms could be alleviated by reducing the dose or prolonging the infusion time.

The lack of disease regression suggests that spirogermanium, administered three times per week, is inactive in renal cell carcinoma. These results are similar to the 23% stable disease rate and 77% disease progression rate obtained by Schulman et al (5) utilizing a similar regimen.

REFERENCES

1. RICE L, WHEELER JW, and GESCHICKTER CF. Spirans XXII. Synthesis of 4,4-dialkyl-4-germacyclohexanone and 8,8-dialkyl-8-germaazaspiro (4,5) decanes. J. Heterocycl Chem 11:1041–1047, 1974.
2. SLAVIK M, ELIAS L, MREMA J, ET AL. Laboratory and clinical studies of spirogermanium, a novel heterocyclic anticancer drug. Drug Exp Clin Res 8:379–385, 1982.
3. SLAVIK M, BLANC O, and DAVIS J. Spirogermanium: a new investigational drug of novel structure and lack of bone marrow toxicity. Invest New Drugs 1:225–234, 1983.
4. HILL BT, WHATLEY SA, BELLAMY AS, ET AL. Cytotoxic effects and biological activity of 2-aza-8-germanspiro[4,5]-decane-2-propanamin-8,8-diethyl-*N,N*-dimethyl dichloride (NSC-192965; spirogermanium) in vitro. Cancer Res 42:2852–2856, 1982.
5. SCHULMAN P, DAVIS RB, RAFLA S, ET AL. Phase II trial of spirogermanium in advanced renal cell carcinoma: a Cancer and Leukemia Group B study. Cancer Treat Rep 68:1305–1306, 1984.

CLINICAL TRIALS SUMMARIES

Phase II Trial of 1,2,4-Triglycidylurazol in Patients With Metastasized Renal Cell Carcinoma[1]

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For the Phase II Study Group of the Association for Medical Oncology, German Cancer Society

Only one-third of the patients with metastasized renal cell carcinoma survive > 1 year; most are dead within 2 years (1). No clearly effective chemotherapeutic or hormonal therapy has been established (2).[8] Ineffective systemic therapy justified a clinical phase II trial with the new compound 1,2,4-triglycidylurazol (TGU).

TGU is a derivative of the triepoxide triglycidyltriazinethione. The exact mechanism by which TGU exerts its cytotoxic activity is largely unknown. By analogy with bifunctional epoxides, TGU probably acts as an alkylating agent. In comparison to triglycidyltriazinethione, TGU showed generally higher experimental antitumor activity at equitoxic doses. Anticancer activity has been demonstrated against a variety of ip or sc implanted murine tumors. In a P388 leukemia subline made resistant to cyclophosphamide, TGU achieved remarkable therapeutic efficacy.[8] Against advanced renal cell carcinomas, TGU produced significant antitumorous efficiency. It was consistently shown in three classical phase I studies that the dose-limiting toxic effect of TGU was myelosuppression (3–5). Irrespective of prior chemotherapy and/or radiotherapy, hematological toxicity became severe [World Health Organization (WHO) grade 4] at a single dose of 1000 mg/m^2 or at a fractionated dose of 250 mg/m^2 × 5. Fractionation of the total dose over 5 days did not offer a major advantage compared to a single high dose. For phase II studies a single dose of 600–800 mg/m^2 iv as a bolus injection or a fractionated dose of 200 mg/m^2 × 5 every 4 weeks depending on individual hematologic toxicity and recovery was recommended (6). The aim of this study was to evaluate the efficacy and toxicity of TGU in patients with metastasized renal cell carcinoma.

MATERIALS AND METHODS

Each patient had histologic proof of measurable or evaluable progressive metastatic renal cell carcinoma not amenable to curative surgery or radiation therapy. Other inclusion criteria were wbc count $\geq 4000/\mu l$, platelet count $\geq 100{,}000/\mu l$, serum creatinine ≤ 1.5 mg/dl, serum bilirubin ≤ 1.5 mg/dl, and WHO performance score ≤ 2. Exclusion criteria were previous palliative chemotherapy, presence of brain metastases, and patient age > 70 years. General medical assessment, routine hematologic and chemical parameters, and toxicity notations were done immediately prior to administration of every therapy cycle. The initial assessment of response to treatment was performed after the first two treatment courses and thereafter at 1-month intervals according to International Union Against Cancer criteria.

Drug Administration

TGU was administered by iv bolus injection at a dose of 600 mg/m^2 every 4 weeks.

Evaluation

For the evaluation of response at least two therapy cycles had to be administered. According to WHO criteria objective response was defined as a > 50% decrease in the product of the longest perpendicular diameters of the indicator lesions in the absence of any new areas of malignant disease. Stable disease was defined as a < 50% decrease or a < 25% increase in tumor size. Progressive disease was defined as a 25% increase in any indicator lesion or the appearance of new lesions.

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TABLE 1.—Patient characteristics

Characteristic	No. of patients
Entered	16
Male/female	10/6
Median age in yrs (range): 60 (37-69)	
WHO performance status	
0	2
1	10
2	4
Prior treatment	
Nephrectomy	13
No previous hormonal and/or cytotoxic therapy	16
Metastatic sites	
Lung	13
Liver	3
Bone	7
Soft tissue	7
Other	4
No. of metastatic sites involved	
1	4
2	4
≥ 3	8
Therapeutic response (WHO)	
Stable disease	8
Progressive disease	8
Toxicity	
Hematologic	
WBC count nadir (cells/mm^3)	
≥ 4000	4
3000-3900	3
2000-2900	5
1000-1900	2
Not done	2
Platelet count nadir (cells/mm^3)	
≥ 100,000	11
75,000-99,000	1
50,000-74,000	0
25,000-49,000	2
Not done	2
Gastrointestinal	
Nausea and vomiting	
1	1
2	4
3	11
Neurological	
Transient dizziness	1
Alopecia (WHO)	
0	11
1	3
2	4
Local thrombophlebitis	4

RESULTS

Sixteen patients were entered in the trial; all of them completed at least two courses of chemotherapy. No complete or partial remission was observed. Stable disease occurred in eight patients. Eight patients experienced progressive disease assessed 8 weeks after the start of chemotherapy. Patients with stable disease continued to be treated with TGU until tumor progression (median duration of stable disease, 4 months; range, 3-5). All 16 patients were evaluable for acute toxicity. All patients had nausea and vomiting (median, grade 3; range, 1-3, WHO scale). Antiemetic pre- or co-medication was allowed for the second and the following therapy cycles; at this frequency, the intensity of nausea and vomiting could not be reduced. Wbc and platelet counts were only slightly depressed, but in two patients with extensive bone metastases a marked depression of wbc and platelet counts occurred (grade 3, WHO scale). Cumulative wbc count toxicity could not be documented. In four patients a local thrombophlebitis occurred (table 1). One patient had short-term dizziness.

DISCUSSION

TGU administered at this dose and schedule does not show substantial antitumor activity in patients with metastasized renal cell carcinoma. The fact that no objective tumor remission was observed suggests that the true response rate is $\leq 20\%$ ($P < 0.05$). It is improbable that TGU has a relevant impact on the fateful course of the metastasized renal cell carcinoma.

REFERENCES

1. DEKERNION JB, and BERRY B. The diagnosis and treatment of renal cell carcinoma. Cancer 45:1947-1986, 1980.
2. WAGNER H, POSSINGER K, and WILMANNS W. A phase II study: combination of vinblastine and tamoxifen in metastastic renal cell carcinoma. ZAC 2:5-13, 1984.
3. HANSEN SW, CAPLAN S, BACH F, ET AL. Phase I study of 1,2,4,-triglycidylurazol (TGU, NSC-332488): an early clinical trial group study. EORTC. Proc Am Assoc Cancer Res 25:167, 1984.
4. SOUKOP M, STUART F, CUNNINGHAM D, ET AL. Clinical and pharmacokinetic phase I study on 1,2,4-triglycidylurazol (TGU, NSC-332488). Proc ASCO 3:26, 1984.
5. NICAISE C, ROZENCZWEIG M, CRESPEIGNE N, ET AL. Phase I study of triglycidylurazol given on a 5-day iv schedule. Cancer Treat Rep 70:599-603, 1986.
6. HILGARD P, PEUKERT M, and POHL J. β-Triglycidylurazol (TGU, NSC-332488, I.N.N.: ANAXIRONE): a new chemotherapeutic agent. Cancer Treat Rev 11:115-120, 1984.

CLINICAL TRIALS SUMMARIES

Phase II Study of Recombinant Gamma-Interferon in Patients With Advanced Nonosseous Sarcomas

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During phase I clinical studies of human recombinant gamma-interferon (rIFN-γ; Genentech, Inc), Kurzrock et al (1) observed minor regression (26%-49%) of lung nodules in a patient with metastatic sarcoma who had received multiple previous chemotherapy regimens. In another phase I study of this same product, Vadhan-Raj et al (2) observed one minimal regression ($< 25\%$) of skin lesions in an AIDS (acquired immunodeficiency syndrome) patient with Kaposi's sarcoma. With these hints of antisarcoma activity we decided to perform a phase II study of rIFN-γ in patients with advanced nonosseous sarcomas.

MATERIALS AND METHODS

Between May 23, 1985, and January 7, 1986, 16 patients with incurable, histologically confirmed, advanced nonosseous sarcomas were treated with recombinant rIFN-γ (Genentech, Inc). All patients had objectively evaluable disease, expected survival of at least 3 months, and Eastern Cooperative Oncology Group (ECOG) performance status of 3 or better. All patients had total leukocyte and platelet counts of at least 3000/μl and 100,000/μl, respectively, and serum creatinine ≤ 2 mg/dl. No patient with serum direct-reacting bilirubin > 0.3 mg/dl was accepted. No significant infections or other malignancies were present, and no significant heart disease was present. No patient had previously received any type of interferon treatment. Patients were not allowed to receive aspirin or other nonsteroidal anti-inflammatory agents, corticosteroids, cimetidine, barbiturates, cardiac drugs, or other antineoplastic agents or investigational drugs during the time on study.

Each patient was scheduled to receive daily treatment im with 0.25 mg/m^2 of rIFN-γ during the first week, followed by this same treatment in daily doses of 0.50 mg/m^2 for the 7 subsequent weeks if tolerable.

Patients experiencing stability of disease or objective tumor regression at the end of the 8-week trial were eligible to receive continued rIFN-γ. Patients who experienced disease progression were taken off the study. Patients with mild toxic effects from rIFN-γ continued treatment in full doses; however, more extensive toxic effects led to temporary or permanent withholding of treatment. Traditional criteria for objective tumor regression, disease progression, and disease stability were utilized in this study.

RESULTS

Among the 16 patients, 11 had sarcomas arising in somatic soft tissues and five had sarcomas arising in visceral sites (table 1). All had received surgical treatment and ten had received radiation therapy for their sarcomas. Fourteen of the patients had received prior chemotherapy (multiple regimens in ten) and one other had received tamoxifen.

Leukocyte count nadirs ranged from 1100 to 5300/μl (median, 2200/μl), and platelet count nadirs ranged from 72,000 to 297,000/μl (median, 196,000/μl). No infectious or bleeding complications were observed secondary to myelosuppression. Fatigue, myalgia, chills and fever, anorexia, and transient rises (to 2-3 × normal) in serum transaminase levels were commonplace; however, no patient withdrew or was removed from study because of drug toxicity. Dose reductions were required in eight patients to alleviate toxic effects. Two patients required dose reductions because of leukopenia and severe fatigue; six others never were able to receive full 0.5-mg/m^2 doses of interferon because of leukopenia in four and fever in two. Five of these six required even further dose reductions (leukopenia, three; high fever, two), and two of them had, respectively, two and three further reductions below the starting dose of 0.25 mg/m^2. One

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TABLE 1.—Sa

Age (yrs)	Sex	ECOG performance status	Tissue origin*	Histologic type (grade)†	Prior therapy‡	Tim prog (
45	M	0	R. leg	MFH (4)	Surg, chemoRx (single trial)	56
56	M	1	R. scapular area	MFH (3)	Surg, radRx, chemoRx (single trial)	28
68	M	1	R. thigh	MFH (3)	Surg, radRx, chemoRx (single trial)	56
30	F	1	R. shoulder	MFH (3)	Surg, radRx, chemoRx (single trial)	28
48	F	0	I. vena cava	Leiomyosarcoma (2)	Surg, chemoRx (multiple trials)	60
26	F	1	Stomach	Leiomyosarcoma (1)	Surg, tamoxifen	37
54	F	0	Mesentery of sm. bowel	Leiomyosarcoma (3)	Surg, chemoRx (multiple)	63
61	M	1	Stomach	Epithelioid leiomyosarcoma	Surg, radRx, chemoRx (multiple)	69
54	M	2	L. popliteal fossa	Liposarcoma (3)	Surg, radRx, chemoRx (multiple)	56
48	M	1	Retroperitoneal	Liposarcoma (2)	Surg, radRx, chemoRx (multiple)	29
26	F	1	R. diaphragm	Fibrosarcoma (3)	Surg, radRx, chemoRx (multiple)	29
44	M	1	R. arm	Undifferentiated spindle cell sarcoma (4)	Surg, radRx, chemoRx (multiple)	28
22	F	0	L. buttock	Synovioma (4)	Surg, radRx, chemoRx (multiple)	73
35	M	3	Base of skull	Malignant schwannoma (4)	Surg, radRx, chemoRx (multiple)	27
59	M	1	L. temporal soft tissue	Malignant hemangiopericytoma	Surg, RadRx, chemoRx (multiple)	67
22	M	0	R. leg	Mesenchymoma (4) (hemangioperi & mesenchymal chondrosarcoma	Surg, radRx	28

*R. = right; I. = interior; sm. = small; L. = left. †MFH = malignant fibrous histiocyto
§Stab = stable disease; prog = disease progression. ¶AST = serum transaminase; alk p

1.—Sarcoma patients treated with rIFN-γ

Time to prog (days)	Survival time (days)	Best objective response§	Wbc count nadir (/μl)	Platelet count nadir (/μl)	Other toxicity¶	Dose reduction
56		Stab	5300	209,000	Fatigue, myalgia, chills & fever, ↑AST	No
28		Prog	2400	211,000	Fatigue, myalgia, chills & fever, ↑AST	No
56	110	Stab	2300	144,000	Fatigue, diarrhea, anorexia, chills & fever, ↑AST	No
28		Prog	2200	197,000	Fatigue, chills & fever, ↑AST	No
60		Stab	1700	80,000	Fatigue, chills & fever, ↑alk phos & AST (had liver mets)	Yes
37		Prog	2300	235,000	Fatigue, N&V, ↑AST	Yes
63		Stab	1700	154,000	Fatigue, chills & fever, ↑AST & alk phos (has liver mets)	Yes
69	81	Stab	5000	297,000	Fatigue, fever, anorexia, ↑AST & alk phos (has liver mets)	Yes
56	235	Stab	1600	126,000	Fatigue, myalgia, chills & fever, N&V	Yes
29	121	Prog	1600	176,000	Fatigue, myalgia, diarrhea, chills & fever, ↑AST	No
29	134	Prog	1100	188,000	Fatigue, myalgia, chills & fever, anorexia	Yes
28	78	Prog	2100	223,000	Fatigue, chills & fever, anorexia	No
73		Stab	1400	72,000	Fatigue, ↑AST	Yes
27	27	Prog	2200	251,000	Fatigue, fever, ↑AST	No
67	136	Stab	3500	260,000	Fatigue, myalgia, chills & fever	Yes
28		Prog	3000	195,000	Fatigue, myalgia, chills & fever	No

tiocytoma. ‡Surg = surgery; chemoRx = chemotherapy; radRx = radiation therapy.
e; alk phos = alkaline phosphatase; mets = metastases; N & V = nausea and vomiting.

patient with poor performance status died unexpectedly early (on Day 27) apparently as a result of cancer cachexia.

All patients experienced progression of disease from 4 to 10 weeks after beginning interferon treatment (median time to progression, 7 weeks). Half of the patients had died when this summary was prepared (median survival, 19 weeks). No patient experienced even temporary regression; however, in four cases, disease stability persisted for > 8 weeks after treatment was begun.

REFERENCES

1. KURZROCK R, ROSENBLUM MG, SHERWIN, SA, ET AL. Pharmacokinetics, single dose tolerance, and biological activity of recombinant γ-interferon in cancer patients. Cancer Res 45:2866–2872, 1985.
2. VADHAN-RAJ S, AL-KATIB A, BHALLA R, ET AL. Phase I trial of recombinant interferon gamma in cancer patients. J Clin Oncol 4:137–146, 1986.

CLINICAL TRIALS SUMMARIES

Treatment of Advanced Refractory Lymphoma With Teniposide and Lomustine[1,2]

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Five institutions within the Eastern Cooperative Oncology Group (ECOG) evaluated lomustine (CCNU) and teniposide (VM-26) in patients who had failed one attempt at curative chemotherapy. The choice of VM-26 was based on a previous ECOG trial yielding six of 27 (22%) objective responses in such patients (1) and on activity in collected series (2). It was combined with CCNU, a drug with established efficacy in lymphoma, and usually not part of the primary treatment. A similar combination had been tolerated by patients with malignant glioma (3).

MATERIALS, METHODS, AND RESULTS

All patients had biopsy-proven, disseminated, measurable, malignant lymphoma (exception, three with rapidly progressive measurable stage II disease following chemotherapy and/or radiation therapy) and had received a maximum of two previous chemotherapy trials but no prior epipodophyllotoxin or nitrosourea. Pretreatment laboratory test requirements included wbc count $\geq 3500/\text{mm}^3$, platelet count $\geq 75{,}000/\text{mm}^3$, total serum bilirubin ≤ 2.0 mg/100 ml and serum creatinine ≤ 1.5 mg/100 ml, and ECOG performance status of 0, 1, or 2.

Cycles of CCNU (100 mg/m^2 orally every 6 weeks) and VM-26 (60 mg/m^2 iv weekly × 4) were repeated every 6 weeks. Escalations of VM-26 by one-third were required if no toxicity was observed in the preceding therapy cycle. Dose reductions of both agents by one-third were also required if nadir counts were Grade 3 or 4. Toxicity and response were defined by standard ECOG criteria (4).

Thirty-eight patients, 19 men and 19 women, were registered. The median age was 58 years (range, 19–77), and the median performance status was 1. Twenty patients had received prior irradiation; all 38 had received prior chemotherapy and all but four had been treated with doxorubicin. Histologic diagnoses included four patients with Hodgkin's disease (HD) and 34 patients with non-Hodgkin's lymphoma (NHL) (two with nodular poorly differentiated lymphocytic lymphoma, four with diffuse poorly differentiated lymphoma, one with both nodular and diffuse poorly differentiated lymphoma, two with nodular mixed lymphoma, six with diffuse mixed lymphoma, two with both diffuse and nodular mixed lymphoma, two with nodular histiocytic lymphoma, 14 with diffuse histiocytic lymphoma, and one with immunoblastic lymphoma). Six patients were inevaluable, including five with NHL and one with HD. Seventeen patients received only a single cycle of chemotherapy (progressive disease, 11 patients; death, four; withdrawal, one; and psychotic break, one). VM-26 dose was reduced on the third and/or fourth dose in 27 of 34 first cycles and was escalated to 100 mg/m^2 in only one patient. CCNU was given in reduced doses in the second (11 of 19 patients) and third (four of 11 patients) cycles.

Toxic effects were mostly hematologic, with median leukocyte and platelet count nadirs of 2400 and $68{,}000/\text{mm}^3$, respectively. One patient died of sepsis (wbc count $700/\text{mm}^3$) on Day 18 of the first course.

Responses are shown in table 1. Of the 38 patients treated, 33 are evaluable for response: one patient had prior radiation therapy to the only evaluable disease, one patient received chemotherapy 2 weeks prior to being entered on protocol, two patients had septic and/or early deaths, and one patient had a psychotic episode and was taken off therapy. Of the ten responses there were eight (four complete responses and four partial responses) in 29 evaluable patients with NHL (28%), with three complete responses reported in 11 evaluable patients with diffuse histiocytic lymphoma (27%). Of the four patients with HD, two patients achieved brief partial responses and one patient inevaluable for response died with no evidence of disease of a respiratory distress syndrome 5 months after treatment.

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TABLE 1.—Characteristics of responders

Patient						
No.	Age (yrs)	Sex	Histologic type*	Prior therapy†	Response	Duration (mos)
1	33	M	HD	RT, MOPP, ABVD	PR	2
2	33	M	HD	RT, BCVPP, ABVD	PR	1
3	66	M	DHL	RT, COMLA	CR	15+
4	73	F	DHL	RT, CHOP	CR	5
5	70	M	DHL	RT, Mega-CHOP	CR	2
6	57	M	DML	RT, CHOP, COP-BLAM	PR	2
7	40	F	N + D PDL	RT + CHOP	CR	26+
8	36	F	NPDL	CVP	PR	10+
10	58	M	NPDL	RT, CVP, chlorambucil	PR	2
9	60	M	NML	CHOP, chlorambucil	CR	14+

*DHL = diffuse histiocytic lymphoma; DML = diffuse mixed lymphoma; N + D PDL = nodular + diffuse poorly differentiated lymphocytic lymphoma; NPDL = nodular poorly differentiated lymphocytic lymphoma; and NML = nodular mixed lymphoma.

†RT = radiation therapy; MOPP = mechlorethamine, vincristine, procarbazine, and prednisone; ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; BCVPP = carmustine, cyclophosphamide, vinblastine, procarbazine, and prednisone; COMLA = cyclophosphamide, vincristine, methotrexate with leucovorin rescue, and cytarabine; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; Mega-CHOP = mitoguazone + CHOP; COP-BLAM = cyclophosphamide, vincristine, prednisone-bleomycin, doxorubicin, and procarbazine; and CVP = cyclophosphamide, vincristine, and prednisone.

CONCLUSION

Despite some antitumor activity for this combination we conclude that the efficacy (27%) (95% confidence intervals, 6%–61%) is not encouraging in diffuse histiocytic lymphoma since only one remission was durable. The data are inconclusive for HD and other types of NHL. Histologic type-specific phase II or III studies are recommended in future trials.

REFERENCES

1. CHIUTEN DF, BENNETT JM, CREECH RH, ET AL. VM-26, a new anticancer drug with effectiveness in malignant lymphoma: an Eastern Cooperative Oncology Group study (EST 1474). Cancer Treat Rep 63:7-11, 1979.
2. RADICE PA, BUNN PA, JR, and IHDE DC. Therapeutic trials with VP-16-213 and VM-26: active agents in small cell lung cancer, non-Hodgkin's lymphomas, and other malignancies. Cancer Treat Rep 63:1231-1239, 1979.
3. SEILER RW, ZIMMERMAN A, and MARKWALDER H. Adjuvant chemotherapy with VM-26 and CCNU after operation and radiotherapy of high-grade supratentorial astrocytomas. Surg Neurol 13: 65-68, 1980.
4. OKEN MM, CREECH RH, TORMEY DC, ET AL. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

CLINICAL TRIALS SUMMARIES

Mitoxantrone for Carcinoma of the Endometrium: A Phase II Trial of the Gynecologic Oncology Group[1,2]

Hyman B. Muss,[3] Brian N. Bundy,[4] Philip J. DiSaia,[5] and Clarence E. Ehrlich[6,*]

Chemotherapy for advanced endometrial carcinoma remains ineffective. Only a minority of patients respond and such responses are generally partial and brief (1,2). Mitoxantrone, because of its substantial activity in both animal tumor systems and several human tumors (3), was selected for a phase II trial in this disease.

Eligible patients were required to have histologically confirmed recurrent or metastatic measurable disease, performance status [Gynecologic Oncology Group (GOG)/Eastern Cooperative Oncology Group (ECOG)] of 0–2, adequate hematologic function (granulocyte count $\geq 1500/\text{mm}^3$ and platelet count $\geq 100{,}000/\text{mm}^3$), BUN $\leq$ 25 mg/100 ml, creatinine $\leq$ 1.5 mg/100 ml, bilirubin $\leq$ 1.0 mg/100 ml, SGOT $\leq$ 50 IU, and informed consent meeting all federal, state, and institutional guidelines.

Mitoxantrone was given at a dose of 12 mg/m^2, via a 30–45-minute infusion, and repeated every 3 weeks. The dose was diminished for patients having grade 1 myelosuppression prior to subsequent treatment, for those who had grade 3 or 4 granulocyte or platelet count toxicity detected on weekly blood cell counts (GOG, World Health Organization toxicity criteria), and for those with gastrointestinal toxicity. Treatment responses were assessed using standard GOG criteria for response (4).

Nineteen patients, all evaluable for response and toxicity, were entered. Twelve patients had adenocarcinoma, four had adenosquamous carcinoma, two had clear cell carcinoma, and one had endometrioid carcinoma. Patient characteristics are shown in table 1. Seventeen of the 19 patients had chemotherapy and doxorubicin was included in the regimens of nine of these patients.

TABLE 1.—Patient characteristics

Characteristic	No. of patients (%)
Entered	19 (100)
Median age in yrs (range): 64 (27–81)	
Primary tumor grade	
I	2
II	7
III	10
Performance status (GOG/ECOG)	
0	5
1	6
2	8
Metastatic site	
Pelvis only	3 (16)
Outside pelvis	16 (84)
Prior therapy	
Surgery*	17 (89)
Radiation therapy	15 (79)
Hormonotherapy	12 (63)
Chemotherapy	17 (89)
Doxorubicin	9 (47)
Immunotherapy	1 (5)
Results	
Partial response	1 (5)
Stable disease	4 (21)
Increasing disease	14 (74)
Median progression-free interval in mos (range): 1.8 (0–7.9+)	
Median survival time in mos (range): 2.1+ (0.5–17.2+)	
Doses of mitoxantrone	
Median (range): 1(1–11)	
Average: 2.6	

continued

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TABLE 1.—Patient characteristics (*continued*)

Characteristic	No. of patients (%)
Toxicity	
Wbc count (mm^3)†	
< 2000	4 (26)
< 1000	1
Granulocyte count (mm^3)†	
< 1000	1 (26)
< 500	4
Platelet count (mm^3)†	
< 50,000	0
Mild nausea and vomiting	3 (16)
No toxicity	6 (32)
Other major toxicity	0
Septic deaths	0

*Total abdominal hysterectomy/bilateral salpingo-oophorectomy.
† Maximum/patient.

A brief partial response was noted in a 64-year-old woman with pelvic and lung metastases who had had prior doxorubicin therapy. After three courses of treatment she refused further therapy, possibly diminishing her duration of response. Increasing disease was obvious after one dose in ten patients; of nine patients receiving greater than or equal to two doses, four required dose modification on the second course.

Toxicity was mild. Five patients had granulocyte counts $< 500/mm^3$ at some time during their treatment program and three had mild nausea and vomiting.

Our results are similar to those of the Southwest Oncology Group (5) where none of 15 patients with endometrial carcinoma responded, nine having received prior doxorubicin. In this study, a partial response rate of 5% (one response among 19 patients; 95% upper confidence bound for response, 22.7%) was observed. This indicates that mitoxantrone has no major activity in patients with carcinoma of the endometrium who have received prior chemotherapy.

REFERENCES

1. DEPPE G. Chemotherapy of endometrial carcinoma. *In* Chemotherapy of Gynecologic Cancer (Deppe G, ed). New York, AR Liss Publishing Co, 1984, pp 139-150.
2. PEREZ C, KNAPP RC, DISAIA P, ET AL. Gynecologic tumors. *In* Cancer: Principles and Practice of Oncology (DeVita VT, Jr, Hellman S, and Rosenberg SA, eds). Philadelphia, J. B. Lippincott Co, 1985, pp 1013-1082.
3. SMITH IE. Mitoxantrone (Novantrone): a review of experimental and early clinical studies. Cancer Treat Rev 10:103-115, 1983.
4. THIGPEN T, SHINGLETON H, HOMESLEY H, ET AL. *cis*-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix. Cancer 48:899-903, 1981.
5. HILGERS RD, VON HOFF DD, STEPHENS RL, ET AL. Mitoxantrone in adenocarcinoma of the endometrium: a Southwest Oncology Group study. Cancer Treat Rep 69:1329-1330, 1985.

Allergy-Induced Hepatic Toxicity Associated With Dacarbazine

Patients with disseminated melanoma are resistant to conventional chemotherapy. Dacarbazine (DTIC), the most commonly used drug, has an overall objective response rate of only 20% (1). In an effort to improve therapeutic efficacy, postsurgical adjuvant trials were begun in patients at high risk for recurrence. There are no data which support a role for the adjuvant use of DTIC (2). However, these trials do not exclude the possibility that a small subset of patients may have benefited. Because of this, and the fact that in conventional doses DTIC causes only modest hematologic toxicity, many physicians continue to employ DTIC as postsurgical adjuvant therapy in patients at high risk for recurrence. However, over the past few years there have been a number of reports of fatal hepatotoxicity associated with DTIC. We report here another case of fatal DTIC-induced hepatotoxicity and review the recent literature.

CASE REPORT

The patient is a 50-year-old male who had a superficial spreading melanoma (1.25 mm thick) removed from his shoulder in August 1978. Wide re-excision was performed and elective axillary lymph node dissection revealed one of 30 lymph nodes positive. The patient was then treated with adjuvant lomustine (CCNU) every 6 weeks for 12 months.

A routine chest x-ray in August 1983 revealed a nodule which, on surgical resection, revealed melanoma. Metastatic evaluation was negative and the patient was then started on DTIC (500 mg iv daily × 5 days) as an adjuvant. The first treatment was tolerated well, but on the third day of the second cycle the patient developed systemic symptoms of fever, chills, malaise, and profound thirst. The next morning the patient collapsed and was admitted to the Intensive Care Unit. The patient had not received corticosteroids as part of an antiemetic regimen.

On admission, the patient showed signs and symptoms of cardiovascular collapse. In addition, marked hepatomegaly was noted that was not present 3 days previously. The alkaline phosphatase was 248 IU/L (nl, 67–289); aspartate aminotransferase 583 IU/L (nl, 1–48), LDH 4658 IU/L (nl, 70–186), bilirubin 2.7 mg/dl (nl, 0.2–1.2), and creatinine 2.0 mg/dl (nl, 0.7–1.4). The platelet count was normal (160 k), the partial thromboplastin time was 50 seconds (nl, 26–45) and the prothrombin time ratio prolonged (1.22; nl, 0.85–1.12). Fibrinogen was 68 mg/dl (nl, 200–400) and fibrin split products were $> 10 < 40$ mg/ml (nl, < 10).

Over the next few hours, the patient's clinical status deteriorated requiring the addition of pressor agents to maintain adequate blood pressure. A four-quadrant abdominal cavity aspiration was unremarkable. The patient subsequently underwent exploratory laparotomy which revealed 1500 ml of bile-stained ascitic fluid with a moderately enlarged liver and edematous gall bladder. An intraoperative cholangiogram was normal and cholecystectomy was performed; however, the liver was not biopsied.

Postoperatively the patient's status continued to deteriorate as he developed acute renal failure as well as adult respiratory distress syndrome. By the fifth hospital day, the SGOT (2494 IU/L), LDH (3108 IU/L), total bilirubin (14.7 mg/dl), creatinine (7.9 mg/dl), and BUN (52 mg/dl) were all markedly elevated. Further deterioration continued and the patient expired on the seventh hospital day.

At autopsy, the liver weighed 2230 g and exhibited a soft, friable parenchyma. Yellow-tan and yellow-orange areas were seen prominently around larger vascular channels. Microscopic examination demonstrated hemorrhagic necrosis of hepatocytes except for a thin rim of parenchyma about the portal triads. The sinusoids were dilated and distended with rbcs and some central veins were occluded by fibrin thrombus which occasionally extended into the larger hepatic vein.

DISCUSSION

The first convincing report of DTIC-induced hepatic failure was that of Frosch et al (3) published in 1979. This report involved a 55-year-old white female who suffered sudden cardiovascular collapse on the third day of the second cycle of treatment with DTIC. This collapse was associated with a marked elevation of hepatic enzymes. Pathologic examination of the liver revealed massive necrosis around central veins as well as vasculitis associated with marked eosinophilic infiltration.

Over the next 4 years, 12 other cases have been reported which were summarized by Féaux de Lacroix (4). Several similarities are noted: (*a*) DTIC doses ranged, for the most part, from 200–250 mg/m^2 day × 5 days; (*b*) all reactions occurred during the second cycle of therapy and usually on the second or third day; and (*c*) all patients rapidly deteriorated and died. The clinical course was usually marked by nausea, vomiting, and right upper quadrant pain progressing rapidly to circulatory shock. Autopsy findings revealed massive hepatic necrosis, thrombus of small hepatic veins, and frequently revealed a vasculitis associated with lymphocytic and eosinophilic infiltration.

The exact cause of this reaction is unclear; however, an allergic hepatic vasculitis with resultant thrombosis seems most likely. The signs and symptoms that have developed in these patients are consistent with the development of an acute allergic-induced Budd-Chiari syndrome. The development of this reaction during the second cycle of therapy, the eosinophilic vasculitis, and the peripheral eosinophilia all tend to support this mechanism. Another piece of supporting evidence is the report by Cznaretzki and Macher (5) of a patient with similar symptoms who responded to the administration of prednisone.

It is important to stress that adjuvant DTIC therapy in patients with melanoma is not indicated and may be associated with a rare but almost uniformly fatal allergic hepatic veno-occlusive disorder (Budd-Chiari syndrome).

All patients who are treated with DTIC should be closely monitored, especially during the second cycle of therapy, for the prodromal symptoms of fever, chills, and malaise. At the first sign of toxicity, the drug should be stopped and liver function chemistries and a cbc obtained. If significant abnormalities are noted or if the patient's clinical condition deteriorates, corticosteroids should be administered. It will be interesting to observe if this phenomenon occurs also when the drug is administered on single-dose schedules.

REFERENCES

1. HILL GJ, MOSS SE, GOLOMTS FM, ET AL. DTIC and combination therapy for melanoma: III. DTIC (NSC-45388) surgical adjuvant study COG protocol 7040. Cancer 47:2556-2562, 1981.
2. MASTRANGELO MJ, BAKER AR, and KATZ HR. Cutaneous melanoma. *In* Cancer. Principles and Practice of Oncology, 2nd ed (DeVita VT, Hellman S, Rosenberg SA, eds). Philadelphia, J.B. Lippincott, 1985, pp 1371-1422.
3. FROSCH PJ, CZARNETZKI BM, MACHER E, ET AL. Hepatic failure in a patient treated with darcarbazine (DTIC) for malignant melanoma. J Cancer Res Clin Oncol 95:281-286, 1979.
4. FÉAUX DE LACROIX W, RUNNE U, HAUK H, ET AL. Acute liver dystrophy with thrombosis of hepatic veins: a fatal complication of dacarbazine treatment. Cancer Treat Rep 67:779-784, 1983.
5. CZNARETZKI BM, and MACHER E. DTIC (dacarbazine)-induced hepatic damage: possible pathogenesis and prevention. Arch Dermatol Res 270:375-376, 1981.

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Transient Nephrogenic Diabetes Insipidus Following High-Dose Cyclophosphamide Chemotherapy and Autologous Bone Marrow Transplantation

Complications following high-dose (HD) cyclophosphamide chemotherapy are well recognized and include neutropenia, sepsis, hemorrhagic cystitis, and the syndrome of inappropriate antidiuretic hormone excretion (SIADH). We would like to report a case of clinically important dehydration due to a renal concentrating defect following HD cyclophosphamide chemotherapy. Antidiuretic hormone (ADH) levels confirmed a nephrogenic diabetes insipidus which subsequently resolved.

CASE REPORT

A 64-year-old man with small cell carcinoma of the bronchus was accepted for HD chemotherapy. Staging investigations showed hepatic metastases, but liver function tests were normal as were creatinine, urea and electrolytes, isotope bone scan, and bone marrow with trephine. He received induction treatment with doxorubicin (50 mg/m^2), vincristine (2 mg), and etoposide (120 mg/m^2/day for 3 days) all repeated once after 3 weeks. Bone marrow was then harvested and cryopreserved in dimethyl sulphoxide (DMSO). He then received cyclophosphamide, 50 mg/kg/day, on 4 consecutive days with bladder protection using 2-mercaptoethanesulphonate (MESNA) without forced diuresis. Two days later the marrow was reinfused uneventfully.

The day after, routine blood analysis showed a raised urea of 14.1 mmol/L (normal, 2.7-8.4) with a creatinine of 328 mmol/L (normal, 53-124), but normal potassium, sodium, and glucose. He developed increased thirst and polyuria. The urea rose to 28.5 mmol/L with a creatinine of 557 mmol/L. Simultaneous serum and urine osmolalities were 318 and 310 mmol/kg, respectively. There were no recorded episodes of hypotension or sepsis. His medication included metoclopramide, lorazepam, nystatin, chlorpheniramine, and dextropropoxyphene/paracetamol combination. He was treated with iv fluid replacement and oral fluids with a total intake of 5 L/day and output of 4 L/day. Over the next 6 days the urea fell to normal. He then underwent a water deprivation test with measurement of ADH and the results are displayed

TABLE 1.—Water deprivation test

Time	Osmolality (mmols/kg H_2O)		ADH (pmols/L)
	Plasma	Urine	
8.00		245	
9.30	297	255	4.6 (high for osmolality)
10.45		242	
12.20	296	251	4.6 (high)
13.45		255	
15.00	300	259	6.5 (high)
15.43		272	
16.00	DDAVP 0.2 ml iv		
17.15		301	

in table 1. Over the following month his thirst and polyuria gradually improved, eventually resolving completely. His tumor progressed in the liver and he died 5 months later.

DISCUSSION

This patient's fixed urinary osmolality in the face of an increasing serum osmolality and high and rising ADH levels indicates a failure of the kidney to control water loss. The actual osmolality level of the urine (300 mosmol/L) indicates that this is probably a concentrating defect of the distal tubule. Following acute renal failure, a similar defect may be seen, the so-called polyuric phase of renal failure, and this concentrating defect may last up to 10 months. We have no evidence that our patient went into renal failure; he was fully conscious and ambulatory during this time and maintained a good urine output. He did not suffer any serious episodes of sepsis. The most likely explanation therefore is a toxic effect of one of the administered drugs. They included cyclophosphamide, MESNA, and bone marrow with its preservative, DMSO.

Our patient received 55 mg of DMSO, a dose of < 1 mg/kg. Transient renal function abnormalities have been observed in two elderly people given well over 1.5 g/kg of DMSO (1), but no adverse renal effects have been seen in patients receiving cryopreserved marrow (2). Doses of up to 1 g/kg are safe in humans (3). MESNA alone has not been reported as showing any idiosyncratic renal adverse effects with cyclophosphamide.

Cyclophosphamide is principally metabolized by the liver (80%), and its metabolites, some of which are active alkylating agents, are excreted in the urine. In high concentration they cause hemorrhagic cystitis, which can be prevented by ensuring a high urine flow rate or administering MESNA. There have been a few reports of a SIADH developing following cyclophosphamide treatment (5). This effect is seen in doses > 50 mg/kg. It is manifest as hyponatremia and a failure to excrete water. The urotoxic properties of the cyclophosphamide group of drugs have been attributed to acrolein, formed in the renal tubule from aldophosphamide, an active alkylating cyclophosphamide metabolite. In our patient there was a failure to retain water because of a diminished ADH response in the distal nephron. It is clear that very careful attention to water balance following HD cyclophosphamide treatment is critical to patient well-being.

REFERENCES

1. YELLOWLESS PP, GREENFIELD C, and MCINTYRE N. Dimethylsulphoxide induced toxicity. Lancet 2:1004-1006, 1980.
2. O'DONNELL JR, BUNNETT AK, SHEENHAM T, ET AL. Safety of dimethylsulphoxide. Lancet 1:498, 1981.
3. BROBYN RB. The human toxicology of DMSO. Ann NY Acad Sci 243:497-506, 1975.
4. SCHEEF W, KLEIN HO, BROCK N, ET AL. Controlled clinical studies with an antidote against the urotoxicity of oxazaphosphines: preliminary results. Cancer Treat Rep 63:501-505, 1979.
5. STEEL TH, SERPICK AA, and BIOELE JB. Antidiuretic response to cyclophosphamide in man. J Pharmacol Exp Ther 185:245, 1973.

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September 24, 1986

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Intraocular Inflammation From Accidental Instillation of Doxorubicin

According to an Adria Laboratories representative, accidental instillation into the external eye of doxorubicin hydrochloride for injection has been reported to the manufacturer on several occasions [J. Luce (Adria Laboratories), personal communication.] Usually very small quantities have accidentally gotten into the eye. The most severe reaction reported by ophthalmologists to Adria Laboratories previously has been a conjunctivitis lasting < 1 week and so far followed by no long-term effects. I would like to report a case of iritis and corneal changes due to doxorubicin in the eye, to alert physicians to this possibility.

A 30-year-old nurse was withdrawing doxorubicin solution (2 mg/ml) from an iv bottle placed slightly above her head when an estimated 0.5 ml accidentally squirted into her left eye. She began irrigating the eye with large amounts of water and saline within 1 minute. The eye burned and teared for about an hour. For the rest of the day she experienced a feeling of numbness and "strain" in the lateral aspect of the left eye. She was examined 7 hours later and found to have a visual acuity of 20/15 in both eyes without correction and tensions of 10 in both eyes. The eye examination was entirely unremarkable; there was no conjunctival injection.

The following morning when she awoke she noted swelling of the left upper lid, left conjunctival injection, and a discharge from the left eye. She experienced a foreign-body sensation. Later in the day the symptoms improved somewhat but did not resolve. She noted photophobia. The lateral conjunctiva still felt "dry." On examination in the evening, her vision and intraocular pressure were unchanged. The left upper lid was slightly swollen and the left conjunctiva had 2+ injection. The inferior third of the left cornea appeared mildly edematous by back-lighting at the slit lamp and with a very narrow slit beam the anterior corneal stroma in this region showed a fine punctate stippling, which appeared to be a cellular infiltrate. A few larger subepithelial white dots were noted. A few tiny punctate spots of fluorescein uptake were noted (punctate epithelial keratopathy). The anterior chamber showed 2+ cells but no flare. The rest of the examination was entirely normal. There were no vitreous cells and no retinal lesions.

After discussion with representatives of Adria Laboratories and several oncologists, I decided to treat the patient in the standard manner for iritis, with topical dexamethasone sodium phosphate, one drop four times a day, and homatropine to dilate the pupil. This decision was made after learning that steroids have been used for the subcutaneous toxic reactions to doxorubicin, apparently without much benefit but also without harm. The following day the patient was considerably more comfortable. The conjunctival injection had cleared markedly. The corneal cellular infiltrate appeared to have perhaps extended slightly upward to involve the lower two-fifths of the cornea. The anterior chamber reaction had diminished to a rare cell. Specular microscopy at the slit lamp of an area of cornea slightly above the involved cornea showed a normal endothelial pattern. The rest of the examination was unchanged except for the pharmacologically dilated pupil.

Over the following week all of the signs of inflammation disappeared. She continued to complain of mild aching when the pupil was not dilated. This subsided gradually over the following month, and the drops were gradually tapered. When last seen, 6 weeks after the accident, she still complained of some residual photophobia in the left eye, for which she used dark glasses.

Doxorubicin is known to cause severe reactions when infiltrated into subcutaneous tissues. Ocular reactions reported to date have been limited to conjunctivitis. This case demonstrates that a corneal infiltrate and iritis can result from ocular instillation of doxorubicin and that standard treatment for iritis appears to be beneficial.

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September 25, 1986

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Cisplatin-Based Treatment of Adrenocortical Carcinoma

Carcinoma of the adrenal cortex is a rare neoplasm with an estimated annual incidence of two cases per million population (1). An aggressive surgical approach provides disease control for the minority of patients presenting with localized disease. With metastatic or locally recurrent tumor, current therapeutic options, including surgery, radiotherapy, or chemotherapy, remain largely incapable of exerting any significant effect on this disease.

In this report we describe our experience in treating four patients with rapidly progressing metastatic adrenocortical carcinoma (ACC) with a combination regimen of cisplatin (DDP), etoposide (VP-16), and bleomycin (BLEO). Table 1 outlines patient characteristics, extent of prior treatment, sites of disease, tumor functional status, and outcome. All patients had had prior treatment with surgery and had received mitotane for variable periods. The mitotane produced no objective responses, and was discontinued prior to chemotherapy in three patients (Nos. 1-3). Each patient had bidimensionally measurable disease and two patients (Nos. 2 and 4) had hormonally active tumors at the time of initiation of chemotherapy with quantifiable biochemical abnormalities.

Two patients (Nos. 1 and 2) were treated with a total of four monthly cycles of DDP, 40 mg/m^2 iv every day, Days 1-5, and VP-16, 100 mg/m^2 iv every day, Days 1-5. BLEO, 30 U iv, was administered weekly for the first 9 and 12 weeks to Patients 1 and 2, respectively. Patient 3 received 2 monthly cycles of DDP, 40 mg/m^2 iv every day, Days 1-3, and VP-16, 100 mg/m^2 iv every day, Days 1-3. DDP was omitted from Cycle 2 because of moderate renal impairment. BLEO, 30 U iv, was administered on Day 2 of each cycle. Patient 4 received two

TABLE 1.—Patient characteristics and outcome of chemotherapy

Characteristic	Patient No. 1	2	3	4
Age (yrs)	38	35	63	56
Sex	F	F	M	F
Performance status*	1	2	2	2
Hormonally active tumor	Yes†	Yes	No	Yes
Extent of disease				
Locally recurrent	No	Yes	Yes	Yes
Hepatic metastases	No	No	No	Yes
Pulmonary metastases	Yes	Yes	Yes	No
Bone metastases	Yes	No	No	No
Prior treatment				
Surgery	Yes	Yes	Yes	Yes
Radiotherapy	Yes	No	No	No
Mitotane	Yes	Yes	Yes	Yes
Chemotherapy	No	No	No	No
Response‡	CR	PR	PD	PD
Response duration (mos)	12	3.5	—	—

*Eastern Cooperative Oncology Group criteria.

†Urinary cortisol levels elevated at time of initial surgical resection but within normal range prior to initiation of chemotherapy.

‡CR = complete response; PR = partial response; and PD = progressive disease.

monthly cycles of DDP, 20 mg/m^2 iv every day, Days 1–3, and VP-16, 75 mg/m^2 iv, every day, Days 1–3. BLEO, 30 U iv, was administered weekly for the first 4 weeks. DDP, mixed in 250 ml of 3% saline and given over 30 minutes, was administered to Patients 1–3. Aggressive hydration with normal saline was continued throughout the treatment period in all patients.

Formal response assessments, including radiographs, computerized tomographic scans, and measurement of steroid metabolites, were carried out every 4 weeks during treatment. Responses were defined as follows: *complete response* (CR)—complete disappearance of all manifestations of tumor, including normalization of elevated levels of steroid metabolites for at least 4 weeks; *partial response* (PR)—reduction of $> 50\%$ in the sum of the products of the longest perpendicular diameters of all lesions and a $> 50\%$ decrease in steroid metabolites for at least 4 weeks; *disease progression*—increase of $> 25\%$ in measurable disease or worsening of steroid metabolite status. Response durations were measured as the interval from initial response attainment to the time of unequivocal disease progression.

RESULTS AND DISCUSSION

One patient (No. 1) attained a CR after 4 months of treatment, with resolution of an extrapulmonic mass and bilateral pulmonary nodules and no evidence of adrenal steroid excess. Twelve months later, recurrent disease was evident with the development of new pulmonary metastases and an elevation of urinary cortisol metabolite levels. Retreatment with one cycle of DDP, 20 mg/m^2 iv every day × 5 days, and VP-16, 100 mg/m^2 iv every day × 3 days was unsuccessful and the patient died of progressive ACC 18 months after commencing the initial chemotherapy. Patient 2 achieved a PR, defined by complete resolution of bilateral pulmonary nodules and an 80% reduction in the size of several intra-abdominal masses. In addition, there was near normalization of markedly elevated levels of urinary tetrahydrodeoxycorticosterone (TH-DOC) from 5339 μg/ml before treatment to 32.6 μg/ml (normal, 5–15) after 4 months of chemotherapy. At that point the patient underwent surgical exploration with the partial removal of several residual tumor masses. Progressive disease was noted 3.5 months later with re-elevation of TH-DOC levels and increasing intra-abdominal disease. Despite treatment with two monthly cycles of DDP, 30 mg/m^2 iv × 1, and VP-16, 80 mg/m^2 iv × 1, followed by a single cycle of cyclophosphamide, 750 mg/m^2 iv × 1, and dacarbazine 600 mg/m^2 × 1, her disease continued to progress and she died 11.5 months after beginning chemotherapy.

Toxicity in these first two patients was substantial but reversible. Both experienced moderately severe nausea, vomiting, and alopecia. Additional toxic effects included: significant myelosuppression, mean wbc and platelet count nadirs were 1500/μl (range, 900–2100) and 91,000/μl (range, 13,000–178,000), respectively; neurotoxicity as manifested by a moderately severe peripheral neuropathy (Nos. 1 and 2); and moderate ototoxicity—mild to moderate sensoneural loss in the mid- and high-frequency ranges (No. 2). No appreciable nephrotoxicity was seen with mean pretreatment and posttreatment serum creatinines of 0.6 and 0.85 mg/dl, respectively.

Two additional patients (Nos. 3 and 4) did not demonstrate any response to treatment with the combination of DDP, VP-16, and BLEO; toxicity was modest and both patients died within 2 months of the initiation of treatment with progressive tumor.

Information on the efficacy of cytotoxic chemotherapy in ACC is limited, due primarily to the rarity of the disease. In 1979, Merrin (2) noted a partial response, lasting 6 months, in a patient with a single pulmonary metastasis from ACC, treated with single-agent DDP. This was followed by a report from Tattersall et al (3) of objective responses in four patients with metastatic ACC treated with DDP in doses ranging from 100 to 120 mg/m^2. Regression of disease was noted in multiple sites in both hormonally active and inactive tumors. Responses were all partial, and lasted between 3 and 7 months. In 1983, van Slooten and van Oosterom (4) reported two partial responses lasting 18 and 22 months, respectively, out of a total of 11 patients who had been treated with a combination of DDP, doxorubicin, and cyclophosphamide. Based on our prior experience with DDP (5) and the smattering of reports suggesting possible activity of DDP in this disease, we treated four consecutive patients with metastatic ACC at our institution with a DDP-based chemotherapy regimen. VP-16 was included in view of its potential synergy with DDP as demonstrated in vitro (6) and the encouraging results with the use of this combination in a number of neoplasms. Bleomycin was also incorporated, in view of its nonoverlapping toxic effects with the other two agents, and a prior report of the activity of a BLEO-containing regimen in this disease (7).

Both patients who received 200 mg/m^2 of DDP/course demonstrated objective tumor regressions (one CR and one PR), while neither of two older patients whose doses of chemotherapy were attenuated up front because of toxicity concerns responded, and both died rather promptly of progressive tumor. Toxicity was substantial, but largely reversible upon discontinuation of chemotherapy.

At the present time, it remains impossible to define a consistently active single cytotoxic drug or drug combination in ACC. Our present experience and the several prior reports on the activity of DDP or DDP-containing drug combinations in ACC prompt us to suggest that the role of DDP and DDP-based intensive combination regimens should be explored further, most logically in the setting of a large multicenter or cooperative group trial.

REFERENCES

1. HUTTER AM, JR, and KAYHOE DE. Adrenal cortical carcinoma. Am J Med 41:572-580, 1966.
2. MERRIN CE. Treatment of genitourinary tumors with *cis*-dichlorodiammineplatinum(II): experience in 250 patients. Cancer Treat Rep 63:1579-1584, 1979.
3. TATTERSALL MHN, LANDER H, BAIN B, ET AL. Cisplatinum treatment of metastatic adrenal carcinoma. Med J Aust 1:419-421, 1980.
4. VAN SLOOTEN H, and VAN OOSTEROM AT. CAP (cyclophosphamide, doxorubicin, and cisplatin) regimen in adrenal cortical carcinoma. Cancer Treat Rep 67:377-379, 1983.
5. GRAPSKI RT, LOPEZ JA, KRIKORIAN JG, ET AL. Cisplatin chemotherapy of adrenocortical carcinoma. Proc ASCO 5:232, 1983.
6. SCHABEL FM, JR, TRADER MW, LASTER WR, JR, ET AL. *cis*-Dichlorodiammineplatinum(II): combination chemotherapy and cross-resistance studies with tumors of mice. Cancer Treat Rep 63:1459-1473, 1979.
7. HAQ MM, LEGHA SS, SAMAAN NA, ET AL. Cytotoxic chemotherapy in adrenal cortical carcinoma. Cancer Treat Rep 64:909-913, 1980.

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BOOK REVIEWS

Urologic Oncology. Sam D. Graham, Jr., editor. New York, Raven Press, 1986, $74.00, 465 pp, ISBN 0-88167-144-4

This new text, addressing the topic of urologic oncology, has been thoughtfully structured by the editor. The text is divided into four subsections: basic science, clinical science, clinical management, and special problems. Although this is a logical structure in which to present problems current in urologic malignancy, the breadth of subject matter hinders an in-depth discussion by some contributors. Further, the rapid pace of development in certain of the topic areas causes some of the presented material to be less than correct.

Basic Science.—The historical perspective presented in each of these first seven chapters does much to provide an appropriate background for an understanding of progress in each area. The Basic Science section is clearly written and thoroughly referenced. Each of the chapters should be required introductory reading prior to embarking upon a more profound review of the specific topic at hand. However, the rapid pace of discovery since manuscript submissions causes almost every chapter, though correct, to be lacking in current data. This is most evident in chapters 1, 2, and 6. The rate of progress in understanding monoclonal antibodies, lymphokines, and viruses, as well as their relationship to human malignant disease, makes it difficult, if not impossible, to provide timely information in the standard textbook format. The authors do provide substantive fundamental information from which further, in-depth reading can follow.

Clinical Science.—The seven chapters which comprise the section on the clinical science of urologic oncology are timely and present the topics in sufficient detail that the reader will be provided with a reasonable understanding of the subjects under discussion. Furthermore, the rate of progress in each of these areas has been such that the subject matter remains current. Each of these chapters is sound and complete.

Clinical Management.—This section of some ten chapters provides a reasonable introduction to the problems which are current in the management of malignant disease of the various organ sites discussed. However, since it is only 180 pages in length, the controversy in management has been avoided. with only results documented. Little is provided in the way of specifics, but much is provided with respect to the results of current management plans. The chapters are thoroughly referenced and thus the reader has the opportunity to pursue a specific topic in depth. Two chapters are devoted to the topic of prostatic carcinoma, one chapter addressing the use of interstitial radiation therapy and the next chapter addressing the topic of surgical therapy. It seems strange that the editor has excluded a discussion of the use of external-beam radiation therapy in the management of prostatic malignancy, as this may be the most commonly applied treatment. The authors of these ten chapters on clinical management provide a sufficient amount of surgical technique and description to allow the reader an understanding of the surgical anatomy and the technical problems involved.

Special Problems.—This final segment of the text is a potpourri of topics appropriate to urologic oncology. With one exception, each of these chapters is timely and current. The chapter on genitourinary prosthetic devices is outdated, reflecting the rapid pace of progress in this area; it is of historical value but fails to provide current concepts.

In summary, the text *Urologic Oncology* is a sound introduction to the field. Touching a broad range of subjects pertinent to the management of genitourinary malignancy, the authors have prepared a well-referenced primary text that would be well placed on the student's bookshelf.

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November 10, 1986

Minimal Residual Disease in Acute Leukemia 1986. A. Hagenbeek and B. Löwenberg, editors. Dordrecht, Martinus Nijhoff Publishers, 1986, $76.50, 393 pp, ISBN 0-89838-799-x

This volume comprises 36 individual papers presented at a conference with the title name, held a year ago. Utilizing direct offset printing the editors have succeeded in publishing the conference content very rapidly. There are four sections, including: detection of "minimal residual disease" (MRD) in acute leukemia; intensive chemotherapy regimens for residual disease in acute myeloblastic leukemia; intensive chemotherapy regimens for residual disease in acute lymphoblastic leukemia; and autologous bone marrow transplantation for the eradication of MRD.

The conference organizers have assembled an excellent group of research scientists from around the world in an attempt to update the progress in the field since the first publication of a previous volume. However, their good intentions of rapid production have resulted in a publication of very uneven quality and somewhat disappointing for those interested in this important aspect of the management of the acute leukemias.

Of the four sections, I found Part I to be the most stimulating and provocative. Clearly, methods of detection have been developed, including the application of monoclonal antibodies, DNA rearrangements through parameter flow cytometry, breakpoint analyses, oncogene patterns on specific chromosomal loci, and important cytogenetic alterations. Issues of sensitivity and specificity are raised by most of the authors. For example, Van Dongen discusses with great clarity the problems of quantification of CALLA in normal and remission bone marrow. Delwel describes the absence of AML-unique surface markers but shows that with FACS "surface" profiles of AML cases could be developed. Moreover, it appears that AML-CFU phenotypes are different from CFU-GM (normal counterparts). The potential exists for detection down to 0.1%.

From this excellent beginning, the remainder of the conference and book is devoted to a review of many clinical trials of AML, utilizing intensification and allogeneic and autologous bone marrow transplantation. Virtually all of these studies represent minimal updating of previously published reports or presentations at major national meetings. This book may be of some value to those investigators who are entering this field for the first time, as it provides a wide overview of the state of the science of detecting and of treating "MRD" in the mid-1980s.

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November 10, 1986

ANNOUNCEMENTS

Position Vacancies: Senior Investigator, National Cancer Institute

The Investigational Drug Branch, Division of Cancer Treatment, is seeking physicians for positions at the Senior Investigator level. We are recruiting physicians who have an interest in the development of biologics in cancer therapy. These positions provide an opportunity to spend from 1 to 4 years working on all aspects of the clinical development of biologic agents. The Senior Investigator will have extensive interaction with extramural investigators and will formulate and implement scientific developmental plans for several agents.

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For further information, contact: Daniel F. Hoth, MD, Chief, Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, Landow Bldg, Rm 4C09, Bethesda, MD 20892 (telephone: 301-496-5223).

First Eastern Clinical Hyperthermia Symposium and Workshop

Philadelphia, Pennsylvania, April 1–3, 1987

For further information, contact: M. Heinrich Seegenschmiedt, MD, Registration Chairman, Department of Radiation Oncology and Nuclear Medicine, Hahnemann University, 230 N Broad St, Mail Stop 200, Philadelphia, PA 19102–1192 (telephone: 215-448-8410).

Symposium on Urologic Cancer: A Post-graduate Update

Baltimore, Maryland, April 3–4, 1987

For further information, contact: The Program of Continuing Education, University of Maryland School of Medicine, 10 S Pine St, Suite 300, MSTF, Baltimore, MD 21201 (telephone: 301-328-3956).

American Radium Society Sixty-Ninth Annual Meeting

London, England, April 6–10, 1987

For further information, contact: Ms. Suzanne Bohn, Executive Secretary, American Radium Society, 925 Chestnut St, Philadelphia, PA 19107 (telephone: 215-574-3179).

Prediction of Tumor Treatment Response

Banff, Alberta, Canada, April 21–24, 1987

For further information, contact: Meg Keiser, Conference Secretary, American College of Radiology, 925 Chestnut St, Philadelphia, PA 19107 (telephone: 215-574-3153).

International Conference on Reproduction and Human Cancer

Bethesda, Maryland, May 11–13, 1987

For further information, contact: Drs. John J. Mulvihill (Landow Bldg, Rm 8C41) or Richard J. Sherins (Bldg 10, Rm 10N234), National Institutes of Health, Bethesda, MD 20892; or call Conference Manager, Ms. Mary E. Clark (telephone: 301-589-6760).

Critical Issues in Tumor Microcirculation, Angiogenesis and Metastasis

Pittsburgh, Pennsylvania, June 8–12, 1987

For further information, contact: R. Hilda Diamond, Associate Director, Biomedical Engineering Program, Carnegie Mellon University, Pittsburgh, PA 15213-3890 (telephone: 412-268-2521).

Second International Head and Neck Oncology Research Conference

Arlington, Virginia, September 10–12, 1987

For further information, contact: Gregory T. Wolf, MD, Veterans Administration Medical Center, Clinical Studies Office (153), 2215 Fuller Rd, Ann Arbor, MI 48105 (telephone: 313-769-7100, ext 755).

Second International Congress on Neo-Adjuvant Chemotherapy

Paris, France, February 4–6, 1988

For further information, contact: S.O.M.P.S, Hôpital de la Salpétrière, 47 boulevard de l'Hôpital, 75651 Paris Cédex 13, France.

Third International Conference on Adjuvant Therapy of Breast Cancer

St. Gallen, Switzerland, March 3–5, 1988

For further information, contact: Secretariat Prof. H. J. Senn, MD, Department of Medicine C, Oncology Center, Kantonsspital, CH-9007 St. Gallen, Switzerland (telephone: 719-219-KSSG CH).

CORRECTION

In the article "Phase II Study of Lonidamine in Patients With Metastatic Breast Cancer: A National Cancer Institute of Canada Clinical Trials Group Study" by P. R. Band, J. Maroun, K. Pritchard, D. Stewart, C. M. Coppin, K. Wilson, and E. A. Eisenhauer (Cancer Treat Rep 70:1305–1310, November 1986), the last column of table 5 (page 1309) contains the following errors: "(0.05)" and "(0.03)" should be "(5)" and "(3)", respectively.

DCPC Cancer Prevention Fellowship Program (CPFP)

Deadline for Receipt of Applications: **March 16, 1987**

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The Division of Cancer Prevention and Control is accepting applications for CPFP. The primary purpose of this program is to attract individuals from a multiplicity of health science disciplines into the field of cancer prevention and control research. The program provides for:

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- Arrange for official academic transcripts to be sent to CPFP coordinator.
- Arrange for four letters of reference to be sent to CPFP coordinator.

How to Apply

Application packets may be obtained by sending a *POSTCARD* with your name and home address to Ms. Nancy E. Garner, NIH/NCI/DCPC/CCAB, Blair Building, Room 4A01, Bethesda, MD 20892-4200 or call (301) 427-8788. Please do not send any material until after you have read the instructions in the application packet.

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